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FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PUBLIC MEETING

SITE-SPECIFIC STABILITY DATA

FOR DRUG AND BIOLOGIC APPLICATION

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P R O C E E D I N G S

Call to Order/Welcome

MS. TOPPER: I would like to welcome you all to our Site-Specific Stability meeting. I know many of you recognize this setup as an advisory committee meeting, but it was the only way to keep everybody within view without sticking them out in the wings. So we just stuck to the normal table.

We have a variety of expertise here. Once Dr. Williams takes over, he will have everyone introduce themselves. But what I need to do is lay out the rules because this is run very different than an advisory committee meeting.

The first thing is, in your agenda, second-to-last page, you will see an open mike page. After we have had all of the speakers who requested time to speak, we will take a very brief break, and we will start on time whether or not you are back. Then it will be your opportunity, those of you who are sitting in the general audience, to ask questions.

In order for our transcriber to get this correct, because we are required by law to have a verbatim transcript, we are asking that you either provide a business card or fill that form out if you don't have a business card with you the first time you come up to ask a question.

If you come up repeatedly, just repeat your name and that will be fine. We will have it spelled right and we will have you credited to the right company, people, organization or whatever.

Legally, the only people that may ask any questions are the people who are seated at the table. We have made the determination because we really do want this to be an interactive process that questions may be asked from the floor. They might not be answered, but they may be asked. We would be more than happy to take the question.

Frequently, you ask questions that we have no control over and we are not going to say, "Oh, yes; we are going to do that," when that is not something we control.

The breaks are very brief. The reason is that this is the beginning of passover and we are making every effort to abide by the religious beliefs that different people in the audience and on our panel have. We will end this meeting at 2 o'clock. So those of you who expect us to run long, like we always do, it is not going to happen today.

I will turn this over to Dr. Williams, now.

Overview and Objectives

DR. WILLIAMS: Kimberly, thank you.

[Slide.]

I would like to welcome you all to the meeting

today which is not an advisory committee meeting but it is a public meeting that FDA looks forward to with some enthusiasm because I see it as an opportunity to really get some good information to help us resolve a difficult issue that I think you all know about, the site-stability issue.

For that reason, I certainly thank you for coming and I, personally, am looking forward to the discussion with a lot of interest. You should all have a handout with an agenda. If you don't, there are ones out at the front desk and you can certainly get copies there. But you can see we have a fairly constrained time period, from 9:00 to 2:00 with a lunch break and a mid-morning break.

So one of my roles, as the moderator-facilitator of this meeting is to keep people on time so that we make sure every voice is heard. We really want to focus on the science and technical aspects of the discussion, recognizing that we have heard a lot of sort of the more general issues and statements from people in the past.

My goal, since I will charge myself to stay on time, is to speak very briefly. I can tell you that, for the most part, this topic is a primary topic for the Center for Drug Evaluation and Research but I also will acknowledge right away that it is of interest to the Center for Biologics Evaluation and Research and, for that reason, you will see that one of the members of our expert panel, or one

of the attendees here at the meeting here today, is Dr. Devine, who is here to represent CBER as well.

Speaking for our center, I can tell you that it is primarily a chemistry topic and, for that reason, we have representatives both from the Office of New Drug Chemistry as well as the Office of Generic Drugs. It also spreads into the world of compliance and the field so, for that reason, we have representatives from the Office of Compliance as well.

[Slide.]

Many of you know that the center--and this also applies to CBER, now, as well, have these coordinating committees that are designed to work on general policy. This particular topic is being handled in the CMC Coordinating Committee of the center. The two co-chairs of that committee are here today with us, Dr. Sheinin and Dr. Holcombe.

You all know that this committee has a very ambitious program in terms of guidances that cover preapproval and postapproval change as well as small molecules and big molecules.

[Slide.]

It is a very ambitious program that, I think, over the next several years will yield a series of guidances that is designed to help pharmaceutical sponsors figure out and

determine what kind of information should be submitted in an application, an amendment or a supplement.

Now, in the fine print, down here, you will see the small word "stability."

[Slide.]

But what that blows up into is a very large stability guidance document. This is a brief history of that guidance document that really began with the NDA rewrite that many of you remember from the mid-'80s. One of the objectives of that rewrite was to create guidances that would be designed to help pharmaceutical sponsors and applicants submit information to the agency.

That was a small dream at that time that, I think, has magnified into a very large effort in many areas in addition to chemistry manufacturing and controls. But, focussing on chemistry for a minute, there were five Red Books that you all know that were produced in 1987. One of them was on stability of human drugs and biologics.

There has been a further effort to update that guidance that, again, I am sure all of you know since you are here in the audience, but it began in 1992. It was interrupted domestically by the ICH effort which you see here resulted in the Q1A, B and C documents.

But then, with the completion of that ICH effort, the Stability Technical Committee of CMC went back and

picked up on the domestic guidance and, again, as you all know, that was published as a very large document in June of 1998.

There have been some meetings on the document and the comment period closed on that large domestic stability guidance document in December of 1998.

[Slide.]

Again, the purpose of this meeting is to focus on one very specific issue in that document that has been quite contentious that we call site-specific stability.

[Slide.]

Internally, at the agency, we have a group who is working on this. The names appear here. Some of these people will also introduce themselves as a member of the expert panel in just a second. But this group has been working very hard to come to a resolution of the particular topic that we call site-specific stability.

This hasn't been easy. I think you all know that there have been some fairly vigorous debates about it. But one of the things I want to emphasize is that the agency, I think, is quite willing to work to come to a better resolution. It is certainly that spirit that motivates this particular meeting.

There have been other meetings as well, and also the formation of an expert panel that I will talk about in

just a minute and then introduce at the close of my session.

One of the things that we have done, in addition to having many public discussions about this in internal meetings, is the kind of documents that reflect the willingness to evolve our position. Some of those documents were made available to you on Monday. I apologize for the last-minute character of that availability, but we thought it was better for you at least to see how the agency's thinking was evolving as an aid to help with the discussions today.

I do know it was last minute and I apologize for that but, again, in the spirit of having a good understanding today, we thought we would get it out to you so you could see it.

Basically, there were two documents that were made available on Monday.

[Slide.]

One of them looks something like this. It had a continuing section that added on a few more words. And then, in addition, there was a table that was also made available. Let me speak to these words for just a minute. I think it was an attempt here--sometimes, when you show a lot of detail on a table, you sort of don't get a sense of the spirit or intent of the general approach that the agency wishes to discuss when it comes to site-specific stability.

So the way to look at these words, and I am certainly not going to go through them all in my few brief minutes here, is sort of a position paper, almost like a concept paper, if you will, that delineates the general issues and approaches and then talks about it for drug substance and drug product both from the standpoint of the information needed as well as the timing of the information and then, at the very bottom, it gets into alternative approaches and further research.

Again, I think our hope here is that this will be useful for you to understand in an overview way some of the subsequent discussion. And then, as I also said, accompanying this was a table that further elaborates on the general positions you see in connection with this position statement of concept paper.

One thing I want to say about the table is that it has deletion of a footnote. You will certainly hear more about this in the course of the morning, but if you have a footnote on your table, you have a slightly outdated table and you should get one that doesn't have a footnote on the first page. I think that is available someplace. It is on the handout out there.

[Slide.]

As I conclude what I want to say, I want to talk a little bit about this expert panel and I am going to ask the

panel, after I conclude, to just go around and introduce themselves and say who they represent. But I would like to say a few words about this concept of the expert panel.

I think what we are doing here is a way to reach out and collaborate and work appropriately with stakeholders. I would say the center, and, perhaps, particularly the Office of Pharmaceutical Science in the center, has developed this concept of an expert panel to help us as we deliberate on public policy.

I, personally, have found them very useful. We have them going in other contexts. For example, we had an expert panel help us with the food fasting, food effects, studies approach that we published as a guidance. I would say, first of all, two things about the expert panel. One is we are trying to be very careful to make sure that it is conducted in accordance with all the rules and regulations regarding advisors and consultants.

That is why we are here under the aegis, if I may say so, of Kimberly and our advisor and consultant staff at the agency. It is not an advisory committee meeting but it is a formal public meeting that should accord with all the laws and regulations about advisory committee meetings. To that end, we certainly thank advisors and consultants in the center and specifically Kimberly and her staff for all the effort it has taken to put on this show, if you will.

The second thing that we want to do appropriately is, as we build this domestic guidance and work with the expert panel, we would like to do so in accordance with the agency's Good Guidance Practices Document which you all know. We believe that, in accordance with both approaches, we are fine here.

I am delighted that the expert panel has been able to help us on this. We will continue to work with the expert panel after this meeting and I would say, already, their input and assistance has been highly valuable and will continue to be highly valuable.

As you look at the membership of the expert panel, you will see the names here on the board. As I say, in a few seconds, I am going to ask them to start it and go around the table and introduce themselves. You can see it is a very carefully balanced group that has academic representatives, industry representatives from the trade associations as well as representatives from the agency.

It is for this reason that they are sitting in front of you and they are here to help us in the deliberations this morning.

I don't know that we have any administrative issues to struggle with. You all have the agenda. There will be a mid-morning break. We will try to adhere fairly rigidly to the time frames so that people don't get short-

changed, as it were, before the close of the meeting. We will close promptly at 2 o'clock this afternoon because of the holidays.

Kimberly, let me just turn to you. Is there anything else I should cover before I ask the panel to introduce themselves?

MS. TOPPER: No.

DR. WILLIAMS: If that is okay, then maybe I will start with you, Bob, and ask you to introduce yourself.

DR. SEEVERS: I am Bob Seevers. I am the Chair of the Center's Stability Technical Committee.

MR. FURNKRANZ: My name is Ken Furnkranz. I am also with the Stability Technical Committee. I am with the Office of Generic Drugs.

MR. SHEININ: Eric Sheinin, The Office of New Drug Chemistry.

DR. EGAN: Bill Egan, Acting Director for the Office of Vaccines at CBER.

DR. AUGSBERGER: Larry Augsberger, Professor of Industry Pharmacy and Pharmaceuticals, University of Maryland.

MR. LACHMAN: Leon Lachman, Lachman Consultant Services.

DR. RHODES: Chris Rhodes, Rhode Island.

DR. BYRN: Steve Byrn, Industry and Physical

Pharmacy, Purdue.

DR. PECK: Garnet Peck, Purdue University, the Department of Industry and Physical Pharmacy.

DR. REYNOLDS: Scott Reynolds representing PhRMA.

DR. SOLLER: Bill Soller, Senior Vice President and Director of Science and Technical for the Consumer Healthcare Products Association, formerly the Non-Prescription Drug Manufacturers Association.

MS. MALIK: Karen Malik representing HIMA.

DR. KASUBICK: Rob Kasubick representing the Generic Trade Associations.

DR. WILLIAMS: Thank you very much. Again, I especially thank the expert panel for their help.

Without further ado, I think we will move on to the first speaker who is Dr. Seevers.

Scientific Issues and Examples

DR. SEEVERS: Good morning.

[Slide.]

Because it is a busy day and I have only been given ten minutes, hang on, it is going to be a fast ride.

[Slide.]

For that reason, let's go over our history briefly. We presented our current thinking in the '98 June draft that actually reflected agency practice and was written in the '87 guideline, that site-specific stability

was necessary. We had a meeting with the trades on July 21 on site-specific stability.

The comments came in through last fall, mostly the day before the comment period closed. We had a premeeting with our academic experts in February to bring them into this process. We, internally, began working on some proposed modifications based on the comments we received and the conversation we had with the experts. And here we are today.

[Slide.]

I want to briefly go over the sense of the comments that we received on the guidance. More than 60 entities commented. That is going to be more than a ream of paper sitting on my desk to be organized. Between 2,000 and 3,000 individual comments; everything was covered.

Let's talk about the site-specific comments.

[Slide.]

Twenty-five entities commented on site-specific. The areas were regulatory, scientific, logistical and economic issues and technical issues.

[Slide.]

Let's talk about the scientific comments now. We were told that it was not based on scientific logic, that process validation is all that was needed. I thought that was interesting because, if that were true, then why is it

when I speak with you as individual firms about specific applications, you tell me, "Let's leave the specifications broad for now until we have done ten or twenty batches at the new site. Then we will change them and make them tighter." So I have to question that.

We were told that stability is intrinsic to a drug product, that site change is less critical than scale-up which requires no stability data. I thought that scale-up did require stability data, at least on a postapproval basis, that there were inconsistencies between NDAs and ANDAs and that site-specific stability should not be applicable to drug substances.

[Slide.]

There were regulatory comments which I want to acknowledge but pass over this morning because we are trying to focus on the scientific issues, that it was contrary to the ICH, that it was inconsistent with FDAMA, that ICH allows pilot batches to support a conservative expiration date; therefore, there was enough wiggle room and site-specific stability would not be needed.

The agency disagrees with those points. We will let it go at that.

[Slide.]

Logistic problems; that it was burdensome, that it was going to cost extra money. Often, a new plant being

built would have to be built as much as a year earlier, that it was excessive to ask for three batches for complex dosage forms and what was a complex dosage form anyway, because we hadn't defined it; that we needed to define the term "intrinsically unstable," and, as I said, define complex dosage forms.

The problem that we were asked is, "Where is the data? What percent of the times that a new plant is used to do a drug is there a problem on stability?" I am here to confess to you right now that I have neither a numerator or a denominator for that.

Let me tell you why, what happens. All too often, according to private conversations I have had with those from industry, when batches are made at a new site and put on stability and they fail, the data is kept internally and never submitted to the agency. It may be seen on an inspection, but that is not likely.

Like surgeons, you bury your mistakes. Therefore, we don't have access to a numerator or a denominator. What I do have and what I am going to use most of the rest of my time for are a number of examples of the kinds of things that we have become aware of and can show you that there are, indeed, problems that have happened.

[Slide.]

The first example is some immediate-release

tablets. They had a 24-month expiry at the original site. Three tech-transfer lots failed or had a borderline assay at fifteen months. The expiry was then reduced to twelve months at material made at the new site.

In addition, a biostudy showed that material from the new site was not bioequivalent. What this illustrates is that site-specific stability is another measure of the sameness of the material made at a new site.

[Slide.]

My second example is an IND capsule drug. It was manufactured at a pilot plant at a non-U.S. facility. Sometimes, we have been accused of jingoism, that this was concern about sites moving off U.S. soil. In this case, the reverse happened. The IND capsules were fine. When they moved to a commercial facility in the United States, it was not packed properly.

This question came up at the AAPS on Monday when I was speaking as to whether packaging could be a problem with site-specific stability. This is an example of exactly that. The blister packaging delaminated. The stability was compromised; poor heat sealing at the U.S. facility. Note that these passed release.

[Slide.]

The next example; an injectable combination drug with epinephrine. At the new site, we found out that they

were adding an overage, first 8 percent and then 11 percent. Why? The failures were in loss of the assay of epinephrine. The stability expiration date went from 36 months to 24 months to 18 months.

[Slide.]

Example 4; preapproval site change for immediate-release tablets. They were hygroscopic. Domestic manufacturing site moved off U.S. soil to Puerto Rico, significantly shorter projected expiry. Puerto Rican site withdrawn.

[Slide.]

Next example. We are going to really fly through these because I want to keep on time but I want to share as many of these as I can. Here is an example that is a site renovation. It is the same site. They renovated the site. The batches submitted for the original application in blisters had satisfactory data on many lots out to 60 months on long-term stability.

After the renovation, it was failing at two months accelerated. The firm has still not been able to explain that.

[Slide.]

An inhalation solution in blow-fill-seal ampules. All specifications met at release. They darkened over time. What happened? They resoldered a head filler on the ampule

fill line and some of the metal was leaching out and catalyzing a color change reaction.

[Slide.]

Antibiotic; failed assay on stability. What was the problem? A new stainless-steel holding tank. The tank was leaching heavy metals catalyzing degradation.

Hang in there. There are only a couple more that I have this morning.

[Slide.]

New facility; several lots recalled for subpotency, low preservative. Why? The material, the active and the preservative, was adsorbing to the PBC tubing used to do transfers. The problem was previously detected at the former manufacturing site but they never got around to telling the new manufacturing site. Tech transfer is not always perfect.

[Slide.]

Example 9. Manufacturing was suspended at the original site after a polymorph was detected. This is happening more and more. As we have compressed review times and industry has compressed development times, things like polymorphs can be overlooked. They subcontracted to a new, clean facility which had never seen a seed crystal of the unwanted polymorph.

Unfortunately, somebody must have brought some in

on his clothing, somehow, and, within a few years, the polymorph was also detected in stability at the new site.

[Slide.]

Last example. An enteric coated tablet transferred from a pilot to production. The pilot stability studies showed 18 months expiration dating period. The production lot failed dissolution at three months.

[Slide.]

What is the take-home message? First, technology transfer is a complex, difficult time-consuming process and there are times when it is not perfect. We all acknowledge that. Second, process validation is a critical method for determining when tech transfer is not 100 percent successful. However, process validation does not give us all the answers. If it did, you would not be asking the agency to maintain broad specifications on new sites until ten to twenty batches had been made.

When site-specific stability does, when we ask for it--and you will note from the tables we are not asking for it in every single case at the time of an application. What it does is it tries to catch those situations.

I am going to turn it over to Ken who is going to who is going to do a little explication of the tables.

MR. FURNKRANZ: Thank you.

[Slide.]

Very briefly, the revised site-specific stability approach reflects that the site-specific stability are needed, as they are being generated now, and the question is the timing of the site-specific stability. It reflects a three-tiered approach.

[Slide.]

Table 1; first of all, we are basing these on the potential to have an adverse effect on the drug substance or product due to site transfer. There are three categories; major, moderate and minor and the timing of the data submission is based on where those products fall in.

The second is the type of product. So table 1 reflects the timing of the submission and tables 2 reflect drug substance and the drug-product categories.

That is all I am going to say. You have those tables in your packets.

Thank you.

DR. WILLIAMS: Ken and Bob, thank you very much. Thank you for keeping as close as you could to the time frame.

I will go right on to Dr. Byrn who will be speaking on behalf of academia and CBER.

Academic Viewpoint

DR. BYRN: Roger and Ken asked me to summarize the premeeting of the academic experts that was held about a

month ago.

[Slide.]

This is a list. You saw a list of the academic experts in the handout. Chris actually sent his regrets at the last minute, but I am sure he will have input today. The other four of the experts were there during the meeting.

[Slide.]

We addressed and spent most of the day, essentially a whole day, addressing these questions which were framed by the agency. Question 1 is, can or does a site transfer affect the quality and/or performance of a drug product. And we addressed these answers yes, no, possibly or maybe. And then why or why not. So that is the first question that was addressed.

The second question, if they answer to 1 is yes, or possibly, what are the factors that can or do potentially affect the quality and/or performance of the product. I think this is the main issue today, really, is what are the factors, when do they come into play.

[Slide.]

The third question is, if the answer to 1 is yes or possibly, how can a firm demonstrate sameness of drug product before and after a site transfer. These are the different ways that we discussed that this could be done, through a technology transfer study, through process

validation of production batches, through release testing of site-specific batches, through stability testing of site-specific batches, through a bioequivalence study or a combination or some of all of the above.

[Slide.]

If one of the answers to question 3, which is the one that I just enumerated, is yes, then we were asked to outline what are the circumstances under which stability studies can be waived or deemed unnecessary prior to approval and marketing of the drug product; that is, what can be done to waive site-specific stability requirements.

[Slide.]

This slide really summarizes the factors that we discussed. This is my second-to-last slide so we are going to have a lot of time at this discussion. This summarizes the factors that we discussed in light of those questions. The first question, or first factor, that we discussed extensively is that stability includes both chemical and physical stability.

That was already addressed by Bob Seevers. As he pointed out, there are some very famous recent examples of physical instability that are in issue that needs to be considered.

Secondly, we had extensive discussion of the examples that were just presented and a discussion of

circumstances and analysis of those examples. One of the concerns in the discussion is that site-specific stability requirements are a catch-all for changes in environmental conditions. This was also pointed out by Bob; for example, change in relative humidity that might occur, changes in the presence of seeds and other environmental conditions involving materials handling or processing.

Another factor that the committee considered extensively was this concept that has already been presented that other changes not controlled in the original validation could come into play, and these changes, the reason they weren't controlled in the original validation is they were not foreseen.

Another factor that was in the minds of many of the academic experts were statements at the BACPAC meeting that basically went like this; you analytical chemists told us these two drug substances were the same. We manufactured them into drug products and they perform differently on use tests, either dissolution or stability. Why is that and what is involved?

Another factor that needs to be considered, although this doesn't happen very often, there are cases where the drug substance changes upon formulation; for example, what you would call in situ salt formation. Under those circumstances, the drug product is different, at least

somewhat different from the drug substance.

[Slide.]

So these were the factors that the academic experts considered. We had a lot of deliberation. What we basically suggested raised the question, and I think it is something important to discuss, are there circumstances under which, even considering all these factors, we could waive stability studies.

The thinking was, and maybe we can have some kind of decision-tree breakdown where we can, for example, say, okay, we have a highly soluble, low permeability drug, known to be stable under stress. Well, then we don't need site-specific stability on that material.

If we have a very unstable compound, chemically or physically, maybe it is necessary to have site-specific stability.

So that was the summary of our discussions and I think you see the table that has been written by the agency based on that discussion. I think probably, in the interest of time, I should go ahead and stop and we can just move ahead.

DR. WILLIAMS: Steve, did you want to take time for some questions now? Was that the end of your presentation?

DR. BYRN: That's the end.

DR. WILLIAMS: As a matter of fact, we did gain about ten minutes there. I will turn, perhaps, to the expert panel to see if they have any comments or questions for Steve. If not, I will turn to the audience.

DR. BYRN: Does anybody on the panel want to add anything, from the academic experts?

DR. SOLLER: Bill Soller. I just have a question in terms of the dialogue that you had in developing your comments. Was this based on your general experience or did you bring case examples to bear looking retrospectively at changes? I am just curious.

DR. BYRN: Sure. Everybody came with their own background in stability. So a lot of discussion came from their own background but, also, the presentation which you saw essentially, all those slides that Bob made on the examples. Those were also considered.

DR. SOLLER: That was basically the universe that was brought to bear?

DR. BYRN: Right. As Bob said, one of the problems, and this is an area that I think PQRI could work in extensively. One of the problems is we don't have a large database to work from in this field, a large scientific database. So the more data we have, the better. We don't have the numerator or the denominator.

DR. EGAN: Did the highly stable types of

molecules that you considered also include proteins and other biotech products which could be thermally stable, for example, but could be unstable--

DR. BYRN: Fred Regnier was the person representing that group but I think--

DR. EGAN: Trace enzymes.

DR. BYRN: There was definitely that thinking that there are stable protein and peptide products that would fall under that category. We do have a statement, though, and this relates to the definition of complex drug substances. I think we have to consider that.

DR. WILLIAMS: Steve, I didn't see highly permeable drugs in there. How did that fit in the picture?

DR. BYRN: Actually, we didn't discuss the permeability index that extensively. We really just discussed the concept that we could divide the drugs into categories that were a problem and were not a problem. Maybe that is a better way to leave it rather than exactly how it should be divided because we didn't explore that.

DR. WILLIAMS: Maybe I will ask a question of Bob or the expert panel. I am just trying to clarify the discussion. In the proposal, the table now talks about drug substance. We now have a concept that certain drug substances you don't have to worry as much about and some you do. And then that fits into your scheme of life in

terms of when you might add site-specific stability.

Let me just add one more thing. In terms to the final intermediate, it is sort of not a problem at all. You are really talking about the drug substance, itself, now.

DR. SEEVERS: That's right. If you look at the table, you see that we did not distinguish in putting highly soluble drug substances, going to drug products in a minor category. We did not distinguish between high and low permeability.

DR. JOSHI: Yatindra Joshi from Novartis. It has been said twice here that there is not enough database. What is not clear to me is that the agency should have information about the development stability batches which are generally done at the development center and, also, the commercial stability batches which are done at the commercial center.

So I would think that there should be sufficient database available.

DR. WILLIAMS: Comments from the agency or the expert panel?

DR. RHODES: I would just make one comment. That information may, perhaps, be in the agency. Most of it is not in the public domain. I am not sure how easy, or how difficult, it would be for the agency personnel to go through all the various documents and collate all this

information into one package.

DR. SEEVERS: Thank you, Chris. You said it better than I did and with an English accent, also. In fact, this is one of the proposed projects, a data-mining sort of project for DPQRI. So that, to some extent, is available. It would require a lot of research in the agency, going through a lot of paper, not a lot of electronic database. It is not ready to hand--it is not material that could be pulled together without a major undertaking.

Given the resources that we have, and the commitments that we have made to review goal dates, we have not been able to do that.

DR. WILLIAMS: Did you have a further comment?

DR. JOSHI: I just had a follow up. For every product that is marketed, I would think that the stability should be comparable for both the development and commercial stability batches. So I would assume that most products that are out there on the market, there has been adequate demonstration that the stability is satisfactory.

MR. LACHMAN: I think, on that subject, a lot of the product-development work, early development work, where you do find a lot of these difficulties, are not really reported fully in the development report that is available in the product transfer into production.

So I think a lot of this information stays with the firm who is developing the product. The agency doesn't get this information. That could be a factor here.

DR. REYNOLDS: You mentioned that you had access to these examples when you went through the academic review. How much detail were you able to go through and conduct some sense, even as a paper exercise or root-cause analysis of each of them to really see if the issue was one that could be chased out during development or during process transfer or truly the only way to do this was the one experience in stability.

DR. BYRN: Sure. That is a good question. When I said access, I meant we discussed and asked--again, we just simply asked agency personnel for more detail, for as many details as they had. In a one-day meeting, we didn't have time, obviously, to go into that level of detail.

Again, I think this is where PQRI, based on what Leon pointed out--this is an area where PQRI could facilitate much better knowledge of what is going on by going through and doing some of these studies to find out the root cause, to understand more about these cases. But, right now, we don't have that data available because it is either buried or in confidential files at a company or buried at the agency.

MR. LACHMAN: I think the quality of the tech

transfer and the validations sometimes will not pick up these variations that you don't anticipate to occur on stability such as tanks where the finishes are poor, stainless steel tanks, and other elements that you don't normally pick up on tech transfer.

This is an area where you run into problems on very sensitive drugs, low therapeutic-range drugs, drugs that are impacted by metal catalysis and things of that type.

MR. FURNKRANZ: I think, in all of these examples, it was demonstrated that it was picked up on stability but it wasn't picked up prior to stability. Yes; I would say that most of these things could be picked up prior to it if you knew what to look for. But they weren't.

DR. WILLIAMS: Steve, thank you very much for that presentation. Are we going to get a copy of that? I don't think I saw it in the--good. Also, thanks for the extra time so we could field a few questions.

Industry Viewpoint

In the next section of the meeting, we have about twenty minutes where we are going to ask for brief presentations of about five minutes from each of the represented trade associations who are here with us today on the expert panel.

The first is Consumer Healthcare Products

Association, a new name, and Bill Bradley will be speaking on behalf of the Association--Bill Soller; I apologize.

Consumer Healthcare Product Association

DR. SOLLER: Thanks, Roger, and I know you know me as Bill Soller. Bill Bradley who works in my shop at CHPA has a broken leg and is one week post surgery and so I am substituting for Bill.

Good morning. I am Dr. Bill Soller, Senior Vice President and Director of Science and Technology for the Consumer Healthcare Products Association, previously known as the Non-Prescription Drug Manufacturers Association, a 118-year-old trade association, representing the manufacturers and distributors of non-prescription medicines and dietary supplements.

We submitted detailed written comments to the docket on December 7, 1998. I have several points that I want to make that relate to the post-hearing comment period, our overall perspective and then a comment on ICH Q1A and PQRI.

First, we think that the initially proposed guidelines over-engineered the approach to site-specific stability. We continue to urge a more flexible approach and, although there has been a reproposal of the guidelines, we have only seen those for about one or two days and our Manufacturing Controls Committee has not had a chance to

have a group discussion on that.

So we would support a position where FDA would allow the administrative record on the stability guidelines to be open for sixty or ninety days. We definitely support that so that we can get additional comments into the record, specifically submitted to the docket.

Second, from our perspective, site-specific stability testing requirements, as outlined in the draft guidance, assumes that validated controlled conditions in a given facility do not create products that are identical in stability characteristics to those that are manufactured under identical validated controlled conditions at another site.

My take is that I think you will hear a similar reprise from the other trade groups. Manufacturing conditions are closely controlled in manufacturing sites for drugs and, putting aside special cases, in general, the stability of an OTC product of a standard formulation made with standardized materials by a standard validated process is only affected by the environment conditions inside the manufacturing facility.

These environmental conditions are defined. They are validated. And, therefore, a change in site where environmental controls are the same at the previous site would not affect product stability.

Whether or not the new site is on a contiguous campus or geographically removed by a great distance has no a prior bearing on the stability of the product. If the process, equipment and environment are controlled and validated identically to the previous site, the stability of the product should be expected to be identical.

If the new manufacturing site is validated as to its environmental controls and the product is produced by a validated procedure, there should be no need for site-specific stability testing requirements for a product can be routinely produced and distributed. Of course, the routine stability sampling and testing would continue as at the previous site as a part of the ongoing stability program.

My third point relates to the reproposal. We think the categorical approach taken by the FDA for the minor changes is directionally correct although, as I say, we reserve our final conclusion for the post-hearing comment period. However, we understand that ICH has site-specific stability under Q1A(R), meaning revision, and we, therefore, urge FDA not to finalize this guidance outside the ICH revision process.

Further, we think that FDA should bring PQRI in as a means to insure a scientifically data-driven approach, particularly for the more complex changes. As I have talked with our members, most believe that there have been a number

of site-specific changes that have occurred and the possibility would be for PQRI to have a call for information specifically in that regard, to bring more information for that retrospective or data-mining exercise.

So, in conclusion, we expect that any company that is moving a production site would follow a protocol for undertaking such a task. Guidances to facilitate, not thwart, this process would be helpful but they should be written in the spirit of GMPs, defining overall goals and objectives without overengineering the specific requirements.

PQRI could be extremely helpful in achieving a data-driven solution to the more complex issues. In our discussions today, we think it is important not to lose site of the fact that, if the validated procedures and manufacturing controls for a product are the same at two sites, then stability will be predictable, reproducible and substantially equivalent at both sites.

As we enter the discussion today, there are several from our Manufacturing Controls Committee that are with me who, I hope, could be also available at the microphone for in-depth comments.

Thank you.

DR. WILLIAMS: Bill, thank you very much on behalf of Consumer Healthcare Products Association. I apologize

for the introduction. I was reading the agenda instead of looking at you.

Our next speaker is Dr. Robert Kasubick who will be speaking on behalf of three generic trade associations; GPIA, NAPM and NPA.

DR. KASUBICK: If no one objects, I will just work from here. As Bill mentioned, we really haven't had an opportunity to take a look at your revised that came out on Monday so i can't address those. But the generic industry is, perhaps, a little different from the NCE or to PhRMA in that a lot of stability is already known about the products that we manufacture.

On that basis, we really feel that the process validation is a real critical issue and many of the examples that Bob and Ken addressed looked as if they were the result of a failure to do an adequate process validation as opposed to something that was just inherent to the stability of the product.

So our position is that process validation is a real critical point to what we need to do and that should be the major emphasis as well as the specifications or, a term that I have come to use, the comparability protocol, to say that, at one point or another, for the generics, there is a protocol or a set of specifications that have already been established to say that this product is the same as or

equivalent to one that is already on the market.

If, in fact, those specifications or that protocol is adequate, then that should reflect the product and not the stability.

Finally, of course, is that stability, again, is not an equipment issue provided that the first two items, of course, are taken care of and that it is inherent in the specifications and the validation and not something that comes out of the equipment.

Finally, to address one last point, the generic industries all support the PQRI effort and feel that the continued effort to look at that, the science management should really go a long way towards helping to resolve this and we really are in support of that.

That's all I have. Thank you.

DR. WILLIAMS: Bob, thank you very much. We got a little extra time there.

I will turn, now, to Karen Malik speaking of behalf of HIMA.

MS. MALIK: I would like to keep this brief in that many of our comments are very similar, if not identical, to the comments you have heard from industry. I would like to first state, though, that our experience base--the HIMA experience base is that we have not experienced a case where, on an investigation, we are looking at the

stability data we could tie a change in stability specifically to a change in the site of manufacture.

We do believe that the technical data that is developed supports the manufacturing process that we put in place and that the time to identify those key attributes, the key aspects, of the process is looking at that technical data, that the stability data and the expiration data are defined, again, considering the manufacturing process, considering the key technical attributes, the packaging, the environment, the formulation, itself, and that, as part of the technology transfer and the process validation, not only are we showing conformance to our GMP but we are also showing the reproducibility of that process and providing assurance that we will meet the specs that we established.

Those specifications should be established to insure that we will meet the full dating period. I agree that, looking at some of the examples given today, that it does warrant further investigation. Again, looking at some of those examples, on the surface, it appears that some of those could be due to either inadequate process validations, are the appropriate specifications set for those products.

Again, it does warrant a further investigation. Given that surface view, it is not enough to identify.

The other comment that I would make is that some of the examples certainly point to some inadvertent changes

that could have occurred within a manufacturing site. They are not directly attributable to a site transfer. There, again, your commercial batch, the stability commitment that you make, the ongoing stability program is there to look at the product that is produced by that process.

If you identify the critical attributes, if you put those into your process, you validate your process, you should not see a change in stability due to manufacturing site change. Again, our experience base has not shown us a Case where, simply due to a site transfer, we have had a change in product stability.

Thank you.

DR. WILLIAMS: Karen, thank you very much.

Our last speaker in this session is Scott Reynolds, Dr. Reynolds speaking on behalf of PhRMA.

DR. REYNOLDS: Good morning.

[Slide.]

I thought I would have to spend a few moments today beginning by framing the issue correctly but I don't think I need to do that. I issue of framing the need for site-specific stability truly does have its--or is considered to have its routes in the need for fast, assuring, successful technology transfer.

So I think we can begin to immediately focus on what is the evidence for successful technology transfer. It

is certainly demonstration of a reproducible and robust manufacturing process and one that provides a clear bridge from the product that was used to support the clinical studies to the product that is used in the final manufacturing site.

I think if I just move directly to the second slide here.

[Slide.]

Just to reemphasize this, with the accepted definition of process validation, as a process validation establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics.

I think that definition is consistent with what I presented on the previous slide and, again, demonstrates that process validation is the accepted marker for success of technology transfer.

[Slide.]

At the same time, I think it is important to discuss, very briefly, the limited utility of the accelerated stability that we have available from the site-specific stability requirements.

The first three months of stability data, or three months stability time point, represents only the first time

point in a much longer stability database that exists from the development and R&D and the NDA stability batches and really don't provide the additional information beyond the much more rich collection of data that is presented during technology transfer and process validation linked together with process development.

As such, site stability, again, is simply not a good surrogate to demonstrate effective process scale-up or process transfer.

[Slide.]

While we are challenging the need for site-specific stability, we are certainly mindful of the extreme importance of examining stability as a critical attribute, or an important attribute of the product.

Studying stability really goes all the way back to the early phases of preformulation studies that are done to understand the chemistry of the compound as it performs in the dosage form. In those studies, the chemical mechanisms of degradation are thoroughly examined, the rates of degradation are studied. Those degradation rates, in a preliminary stage, are used to evaluate potential trigger points for subsequent safety qualification of degraded products.

All of these data are used to guide the selection of the product and the storage conditions and, as a result,

specifications for product acceptability can be determined at release and control. These proposed specifications, of course, are in the data package that is used by the FDA to review the NDA.

It is also important to note that this entire range of activities is reviewed with the FDA during the course of the IND process.

[Slide.]

Just as there is a continuum of stability studies, there is a continuum of process development activity all the way from the laboratory to the pilot plant where clinical supplies are prepared and on into the final manufacturing plant. It is during these phases of process development that the appropriate formulation composition is determined, that the appropriate processing conditions are determined and established but the environmental control parameters required to produce that product at any scale, at any site, are also established.

[Slide.]

More importantly, it is during these same early stages of process development that the basis for process validation is established. The selection of the appropriate process equipment, the desired processing conditions, are all established with fundamental studies of the underlying mechanisms that control those processes.

So, if one considers a granulation process, for instance, it is during this early stage of development that the mechanisms for granular growth are examined and studied when the corresponding granular characteristics and the impact of those granular characteristics and the dosage form performance are first examined.

These all lead, then, to the identification of critical quality attributes and intermediates in the final product.

[Slide.]

Subsequent development efforts which lead into process validation then lead to the identification of critical process parameters necessary to assure the product can be produced under reproducible and robust conditions.

To go back to our example of granulation, for instance, it would be during these stages that in-process controls, such as an endpoint granulation measurement, would be established to assure the each and every batch performs the same way to produce the same granules that have the same characteristics in the final product.

As I mentioned earlier, at the beginning of these two slides on process validation, this sequence of activities provides a subsequent scale of plants.

[Slide.]

So, to summarize, the deliverables from that

process validation study, as we have stated, demonstrates reproducibility of the process and equivalence of the product upon scaleup. It is during this final exercise at final scale in the final manufacturing train that the consistency of these critical process parameters are established and the quality attributes of the product are demonstrated.

It is also during this final exercise that one demonstrates the success of any in-process controls which are established for every unit operation to insure control of each and every batch. I think it is important at this time to remember that process validation is really the last stage in a map that you have developed all the way from the early stages of process development through the scale-up studies in a pilot plant and on out into the manufacturing plant.

[Slide.]

We have also heard, in previous meetings and today, that there are certain concerns for the need of site-specific stability related to the concerns about specific variations in control of the local environments at particular manufacturing sites.

As has been described briefly previously today, these really represent GMP issues that are readily addressed and controlled through facility validation. Similarly,

equipment validation on many of these issues can be similarly established.

A firm is obligated to address all of at every manufacturing plant; the facilities, the procedures, the control operations of the plant, the suppliers of raw materials and components of the manufacturer plant, the water systems and other utilities including those that control the environmental conditions within the manufacturing areas are all GMP issues that need to be established and controlled regardless of the site-stability requirement.

Similarly, equipment, qualification, maintenance, et cetera, that we have discussed briefly in some of the examples, are also GMP issues.

[Slide.]

The key issue is really to link the knowledge of process development to the process at the final manufacturing site and use all that information to insure the plant is properly designed and operated. I am sure everybody would agree that if a product requires tight control over humidity during compressing, for instance, then the most robust approach would be to, up front, establish the need for humidity controls, demonstrate the ranges that are acceptable for that product, and build that into the design, operation and manufacturing plant.

That is a much more robust way to demonstrate and control that feature for the life of the product than to simply do one experiment, to go down and do one experiment at the site to establish that that site will always produce material with the same quality attributes.

I think this gets back to the scientific basis for the best approach to insure quality for the product at a manufacturing site for the lifetime of the product. I think the same thing can also be said for process parameters that are monitored during process validation.

[Slide.]

Briefly, and this has been mentioned already before, but it is important to know at the end of the day the characteristics of the product including stability are demonstrated at the final manufacturing site. A firm is obligated to meet stability requirements to place the first three lots up on stability.

Certainly, if these fail, the firm risks recall. So, clearly, the firm has substantial confidence in the stability when they launch the product. In addition, there is the routine issue of testing of every single batch to insure that it meets its predetermined specifications. Lastly, there are ongoing stability studies that monitor the stability of a product for its lifetime.

[Slide.]

So, in summary, successful technology transfer requires thorough process development experience, one that is routed in preformulation and a fundamental understanding of the stability characteristics of the drug product and the drug substance and continues with fundamental studies to best understand what controlling mechanisms there are in the manufacturing process.

The issues of technology transfer related to the specifics of the manufacturing plant need to be addressed through GMPs at every site. Specific requirements for facility and environmental considerations can and should be identified during process development and translated into controls qualified at the final manufacturing site.

A demonstration of process robustness can best be achieved through process validation in that final manufacturing plant.

Lastly, in summary, there appears to be little scientific evidence that demonstrates the utility of site stability as a measure of successful technology transfer and, indeed, a far more powerful tool to assure this is the conduct of a rigorous process-validation exercise.

DR. WILLIAMS: Scott, thank you very much. I would like to thank all the industry speakers for keeping us within our time frame.

We now have a ten-minute break scheduled. I would

encourage everybody to move quickly and be back here at 10:15. Thank you very much for the first part of the morning session.

[Break.]

Presentations by the Public

DR. WILLIAMS: We have nine speakers who have requested time to speak. These people will have formal presentations in addition to the time for more informal discussion this afternoon. The first speaker who is given fifteen minutes is Dr. Dhiren Shah speaking on behalf of Hoechst Marion Roussel.

DR. SHAH: Good morning, everyone.

This morning, when I came to the session, I saw my two major former professors from Purdue, Dr. Garnet Peck and Dr. Steve Byrn. I remember, when I was at Purdue, if my answer did not match with their answer, they took off points and my grades were lowered. I hope, after speaking today, the FDA will not do that.

[Technical difficulties.]

DR. WILLIAMS: Maybe while Dhiren is getting ready, Kimberly wanted me to announce the fact that the domestic guidance comment period has been reopened. It will close on June 14, 1999. Kimberly, do you have a docket number? The docket number is 98D0362. It closes June 14.

In this interest of this technical glitch here, I

wonder if I might ask Jim Curley to go next while you sort that out.

DR. SHAH: It is almost done. Sorry for that glitch.

[Slide.]

What I am going to do is go and share with you HMR's experience with product transfers and extend that to site-specific stability.

[Slide.]

As an outline of my talk, I will briefly provide some definitions followed by FDA's revised site-specific data proposal which came out recently, very quickly look at factors affecting stability of drug substances and drug products, and what I call probably the analysis of manufacturing site change on stability, develop some information, a database for that.

I will review some examples, potential solutions to the issue, conclusions and recommendations.

Looking at definitions, again, I don't want to spend too much time on the definition of stability. It is in the guidance. But the key thing is, within the specification established to insure identity, strength, quality and purity throughout the period. So keep that thing in mind.

[Slide.]

Selection of batches; again, this is from ICH Q1A; the selection of batches is one can use the minimum of pilot-plan scale and that stimulates the final process to be used on a manufacturing scale, should be representative of quality of preclinical, clinical and to-be-manufactured or commercial product.

So that is the definition of selection of batches and site-specific batches. Again, it is in the guidance.

[Slide.]

The site-stability data proposal which was revised by the agency recently, it was shown by other speakers so I won't spend too much time. It is based on major, moderate and minor changes and what type of information should be submitted. Table No. 3 goes into the requirement for drug products.

[Slide.]

Factors affecting stability of drug substances. This is nothing new for us. You can see, starting with, for the drug substances, synthesis, process can affect the stability of the drug substance; equipment used in the manufacture; batch-size scale. Very important; final drug substance purification, recrystallization, drying, milling, if applicable.

This is very critical. The point Dr. Byrn spoke about, polymorphism; most likely, it is controlled at this

stage. In-process controls and methods; SOPs, GMPs, operator training, environmental conditions. Packaging; container-closure system and storage conditions can affect. And, of course, the specs and the methods.

A similar thing can be done for drug products. It is slightly different. It starts with the component composition. That can affect the stability of the drug product. Inactive ingredients; quality and source. Manufacturing process and equipment, batch size and scale, end-process controls and methods; again the same factors, SOPs, GMPs, training, environmental conditions, container-closure system, packaging and storage conditions and specs and methods.

Those are the factors in my mind which can affect stability of drug substance and drug product.

[Slide.]

What I mean by impact probability analysis; this is very similar to SUPAC triangles or pyramids we have seen where you want to see the impact and the probability of a given change. For a drug substance, I envision the company developing a table like this.

One day, you can call this a comparability protocol. It is not a protocol, but take those eight factors and, again, decide, for example--you can add other factors which are applicable to your process and look at the

original site, the new site, and what is the impact and probability.

I would just take an example. For example, for equipment, if it happens to be different at the new site, then the impact may be moderate and the probability will be moderate. Final drug substance purification or drying or milling is different. That is significant, in my opinion, in most cases with high probability.

The same thing with container closure. If you change that, or packaging, that can have an impact. A similar analysis table one can develop for drug product. For drug product, again, you look at those eight factors. For example, inactive ingredient, quality and source is different at the new site can have an impact with a high probability or moderate probability on stability.

Batch size; more than 10X. If the scaleup is more than 10X, then one can have an impact on the product stability. Operator training, environmental conditions, SOPs. If they are different, then it could be significant. So this is a table I propose companies to use to analyze all these factors affecting the drug substance, drug product manufacturing site change.

[Slide.]

I will go through the examples. Since this is a public meeting, I was not allowed by my lawyers to use their

product names or project code numbers, so what I will do, I will just go through examples, several examples on development projects which are in late phase III, some on marketed products.

The details, including data, will be provided to the agency if needed or requested.

[Slide.]

The first example; a stereo-specific synthesis on drug substance, a CNS drug substance, its manufacturing was moved from the U.S. to Europe and we have made a dosage form out of it and we haven't seen any stability difference in drug substance or drug product.

An antibiotic drug substance, semi-synthetic; its first fermentation followed by synthesis. Addition of another site. And we didn't see any change in stability of the drug substance or the injectable drug product.

[Slide.]

A racemic drug substance with polymorphs, identified polymorphs in that it is a nine-step synthesis. We have added another site for manufacturing of that drug substance. We haven't seen any stability changes in drug substance or drug product.

[Slide.]

Here I will go through several examples which will represent different dosage forms, not just solid dosage

forms, not just parenteral drugs but the idea of dosage forms. Antiemetic injection, terminal steam sterilization. The primary NDA stability batches were at a site in Europe and the commercial batches were manufactured in the U.S. No difference in stability of the drug product.

Antibiotic film-coated tablets. It is in phase III right now. The primary stability batches were made in Europe. The commercial batches were made in the U.S. There is no difference so far on stability.

[Slide.]

Lyophilized product for cardiovascular drugs. Phase III clinical supplies and pivotal stability batches were made in Germany and planned launch batches made in Italy. We haven't seen any difference in stability.

[Slide.]

Anti-allergy products which involves a solid dosage form, wet granulation process. And a second product which is combined with a decongestant, a press-coated tablet. Original batches were made in U.S. We transferred to Puerto Rico. No difference in stability.

This is a capsule product, anti-allergy capsule product. The primary NDA batches were made in the U.S. Again, we added Puerto Rico for capacity point of view and we don't see any difference in stability.

[Slide.]

Moving on to ointments. Water and oil-emulsion-type ointments, originally manufacturing in U.S, transferred the product to German and we haven't seen any stability differences.

Extended-release tablets. It is a wet granulation process manufactured in New Jersey. The NDA was approved based on that. We transferred the manufacturing to Cincinnati. No difference in stability.

The last example, extended-release capsule for a cardiovascular drug. It is a multiparticulate system, beads. Again, we have moved from one place to another and we don't see any difference.

[Slide.]

In summarizing my examples, HMR has transferred manufacturing of approximately seventy products with a variety dosage forms between three to four geographical locations including Europe. What we found was that for receiving sites, the transferred products were almost like new molecular entities. They had to be taught the whole process of manufacturing.

As I mentioned earlier, the dosage forms were IR, modified release, parenteral semi-solids. The drug substances involved in the manufacture of those drug products were all different kinds, low solubility-low permeability, low-solubility-high permeability, high

solubility-low permeability and, also, some with polymorphism issues. So those types of drug substances were involved.

The bottom line is there was no impact or change in stability of the dosage forms.

Again, I was talking in the coffee break that we were transferring seventy products. Somebody commented that, "Well, these are marketed products so that doesn't count." But, in my mind, a molecule or a dosage form does not remember whether it is marketed or a new drug. When you transfer it from one place to another, it is a transfer.

[Slide.]

Potential solutions to the issue. I will go to the solutions. About two years ago, there was a workshop sponsored by AAPS and FDA. Dr. Chi Wan Chen and I were comoderators for a breakout session on FDA-industry meetings. We were just going through a brainstorming idea of what should be included in that breakout session.

She mentioned that maybe site-specific stability can be discussed at FDA-industry meetings. So, Chi Wan, I am taking that idea and expanding on it. I suggest that the sponsor and applicant has the burden of proof. At the end of the phase II meetings and/or pre-NDA meetings, discuss the plans for addition of any new manufacturing site.

In some cases, maybe the end of phase II is too

early to decide about the new site, but I am pretty sure that, by pre-NDA time, the company should have a fairly good idea where they want to manufacture their commercial product. So discuss that.

Share and discuss the impact probability analysis tables which I showed earlier. Solid-state forms, polymorphism, surface area, types of dosage form, equipment, et cetera. Discuss the science. Provide pharmaceutics and surrogate data information to prove the ruggedness of drug-substance and/or drug-product manufacturing.

For example, design of experiments. Most companies do this thing, design-of-experiment studies; share the results out of that. Again, that is discussing science. And make a commitment to place the first three batches from the new site on long-term stability and report to the agency. And make a commitment to keep the additional site ready for PAI, preapproval inspection.

[Slide.]

The next solution or suggestion I have is that the agency consider involving the Office of Compliance and district office at the end of phase II or at least pre-NDA or ANDA CMC meetings where the Office of Compliance or the investigators can find out about the additional site and the things which we want to discuss, the impact probability analysis tables. Discuss DOEs and planned-process

validation, emphasis on environmental controls, training, et cetera.

And inspection readiness for the additional site. In general, I think prepare for PAI but, but by involving the district office or Office of Compliance, it will really help if a company wants to add a new site. As a matter of fact, I like this concept.

I was talking with the district office director in Kansas City, Mike Rogers. Even for general preparation for PAI, the agency may want to consider this.

DR. WILLIAMS: Dhiren, are you going to be able to wrap up pretty soon?

DR. SHAH: Yes. Conclusions and recommendations.

[Slide.]

Again, site-specific stability data in the original submission, a requirement in most cases--underlined "most"--is unnecessary and non value added. I ask the agency the consider review of site-stability release data during an NDA-ANDA review cycle.

For biotech products, site-specific data in the original submission may be justified--again, may be justified because of its complex nature.

Exceptional cases; if the manufacturing process and the environment are modified or not controlled, that will result in bad stability. So the exception should not

rule the norm. Examples on seventy products with no change in stability after manufacturing site changes; again, to repeat that, end of phase II, pre-NDA meeting, that is where to discuss and decide how much site-stability data and the submission route based on science--based on science, not on a priori thinking about a given dosage form.

The same thing with the Office of Compliance. Again, remember, site-specific stability must be submitted. But how? This is my proposal. Three-month stability data accelerated on 3 on 3 batches plus standard commitment in a post-approval, CB, supplement with a 30-day wait prior to commercialization for scientifically justified potential significance and major adverse effects of site change.

That is my proposal for major changes. For moderate; three-month stability data on one batch plus standard commitment in the CB supplement with no wait. This is prior to commercialization. And the last one matches with the proposal, six-month accelerated data and long-term multidata on the first three batches for commerce and first and subsequent NDA annual reports for minor changes.

Again, in my mind, the site-specific stability data requirement in the original submission in most cases will result in submission approval delays by six to twelve months. Ask the agency not to regulate the normal situation by exceptions and avoid unnecessary delays.

The real winner will be the patient.

Thank you.

DR. WILLIAMS: Dhiren, thank you very much.

Our next speaker, who also has fifteen minutes, is Dr. Jim Curley of Pfizer.

DR. CURLEY: Good morning.

[Slide.]

One of the advantages of being a little later in the program is that many of the points that I had planned to make others have made, so I can move, perhaps, a little more quickly. I am Jim Curley and I am representing Pfizer, Inc. As you have heard this morning, from Pfizer's perspective, and from others, that the draft guidance that is on site-specific stability goes beyond what is proposed in the ICH and that the concepts of process validation, technology transfer, assure equivalence of product made at different sites and that in-process controls, specifications and annual stability testing provide continuing quality assurance.

That has been a theme we have heard this morning.

Prior to approval, during the development phases, in-process controls and specifications are established to assure product quality. Process validation assures consistent quality standards are met whenever and wherever the product is made. Technology transfer assures that the

same high-quality standards are met at each location.

Prior to approval, the controls and specifications are subject of FDA review and, obviously, approval. The technology-transfer activities are subject to review during preapproval inspection so the agency has accessed this information.

[Slide.]

Others have pointed out that, post-approval, the GMPs assure that a manufacturing facility is suitable and the manufacturing occurs by the approved process in process control and finished goods, testing and reconfirmed product quality and that the ongoing annual stability programs add extra assurance that product continues to be of high quality.

[Slide.]

So, with those factors in mind, it is really unnecessary to have site-specific stability because the other controls are in place and performing unnecessary work adds to product cost and diverts resources from other endeavors.

[Slide.]

I would like to just briefly talk about one product transfer success. I am actually going to present some data from a site-specific stability program that Pfizer ran as part of this transfer of the product. The data I am

going to describe are only the potency data. These data were measured by a valid stability-indicating method.

The results are going to be presented in a normalized basis as percent of initial assay.

[Slide.]

By way of background, this product is a drug substance, an API. It has an FDA-approved specification of 97 to 103 percent for potency. One batch, which was made at the original site, was set up in a head-to-head horse race stability program against three batches from the new site. So site A and site B, three batches.

This product has labeled storage as a bulk at 15 degrees C, so 25 degrees C actually represents an accelerated program. Chi Wan Chen, this accelerated program has four points.

If you look at these data, statistics is not my forte so my simplistic approach for looking at this data was just to combine all these data into one set, regardless of site, whether it was labeled storage or whether it was accelerated storage and to look at that.

[Slide.]

If you look at all those data, the range of potencies is between 98 and 101, and the mean is 100 percent with a standard deviation of 0.5. So this site-specific stability program did, indeed, indicate that there was no

difference between the two sites. But my point is we didn't need to run that program to know that. We had put in place the validation and the controls to assure ourselves that that was going to be the outcome.

But I present this as an example of when things go right.

[Slide.]

Just to come to the conclusion, since many others have made these points earlier, these factors assure equivalence of product; CGMPs process validation, technology transfer, in-process control and finished-goods testing in the annual stability program.

[Slide.]

Pfizer appreciates the opportunity to discuss this topic and the hope that we can keep talking about this very important subject.

Thank you.

DR. WILLIAMS: Jim, thank you very much. Thank you for bringing us back on time.

DR. CURLEY: You're welcome.

DR. WILLIAMS: Our next speaker, who has ten minutes, is Dr. Robert Jerussi of Jerussi Consulting.

DR. JERUSSI: Thanks for the opportunity of speaking here. I want to talk about the generic-drug industry's contribution to the site-specific stability

debate. I am not representing the generic industry. I am representing myself and my firm and some of the things I am going to present to you some of you have seen and, perhaps, considered.

But, you know, to get a generic drug approved, you have to do a lot of work at specific sites.

[Slide.]

There are twenty-two captopril approvals in the generic industry. They didn't all get to market. In fact, the word is no one made any money out of this drug. But it means that twenty-two different manufacturing facilities produced the pilot batch of at least a 100,000 units.

I can't tell you whether there were twenty-two different manufacturing procedures, but you can bet there were a number of them and you can bet there were a number of formulations and you can bet there were a number of sources of the drug substance.

All of these passed three-month stability in a bioequivalence test to get approval. My search of FDA's data from 1992 to February 1999, on the recall list, none of them have been recalled. I think that says something about manufacturing at different sites.

We have been hearing this morning about environmental factors, equipment factors. These are all different environments and probably different pieces of

equipment.

I would like to go on with the list. This was first presented to me, and to some of you, by Sid Goldstein at Duramed. His name is on the overhead.

[Slide.]

Here is a group of others with multiple approvals. The same thing I said before stands for these. This number were approved. They were made at different manufacturing sites and in only one of these in my search could I find a recall and it was on a cimetidine product for that ubiquitous test, dissolution. They failed dissolution before the expiry period.

Again, they were all made at different sites. Now, one of the things that supports one of the things the committee did in this chart was, as I read this chart, if you had a highly soluble drug, you didn't need any up-front stability data at a new site. I think I am reading that correctly.

Most of these drugs are soluble, what we call under SUPAC, IR definition of soluble. One is not, though, at least from the data that I have and that is acyclovir. That is an insoluble drug. Note that one is a modified-release. You just heard a previous speaker talk about modified release and insoluble drugs not having stability problems.

I intend to follow this up. There is another one that I looked at yesterday, diltiazem, which has a couple of generic approvals and there have been recalls due to dissolution failures.

So what I am saying is that the agency has a lot of data in its own files. I can't tell how many of these were approved--I mean, actually got to market. I can't tell how many of these the companies followed up and went out to two years with their data. So it is difficult for me to say they are all fine.

But the recall data just isn't there for these products and I urge the agency to use the data that they have in the generic-drug area as to whether or not site-specific data is really needed.

Thank you.

DR. WILLIAMS: Bob, thank you very much.

Our next speaker, who has fifteen minutes, is Dr. Tony Amann speaking on behalf of Eon Laboratories.

DR. AMANN: Good morning. I thank you. I want to thank the Expert Working Group on Site-Specific Stability to give us some time in order to express our opinions about this very topic that is so dear to us.

[Slide.]

What I am going to do is come from a little bit different angle and that is not so much from giving you a

series of examples but, more or less, from looking at the historic perspective of where we started, how we got there, where we are now and then certainly come up with a recommendation as I feel is appropriate under the current regulatory environment.

[Slide.]

The general conditions I will review a little bit. I want to give you the original rationale or issue that seemed to have perpetuated, at least in the generic industry, the idea of having site-specific stability, look at the changes in implementations that have occurred since that original rule, certainly address a little bit about the FDAMA impact which is really, certainly, apropos at this stage as well with increasing guidelines, a little bit touch on really what is a GMP issue which could be a district-related type of responsibility versus a submission issue which is really a CDER responsibility and, certainly, at the end, make my recommendation.

[Slide.]

I think the first issue under the old--and I can certainly understand the quandary that FDA was in--the old practice was, over ten years ago, that it is quite possible that you had small dosage units, very small dosage units from site A and, on extreme conditions, take it to a production site B and scale it up, 10, 20, 100 fold.

That, in itself, at this stage of the game, there were certainly some issues.

[Slide.]

What was the environment, at that time, the regulatory environment? First of all, the really was no requirement for any minimum batch size or currently the 10 percent batch size. Certainly, there was not a distinct recommendation or protocols for process validation. Changes in site were ongoing without any issues.

But, along with changes in site, quite often you had change in manufacturing procedure, changes in formulation. Those two have been addressed earlier on. Those things can, and often will, affect the stability of the product. It is all recognized by the industry. Scientifically, there is dispute on that particular issue.

Certainly, there is bulk hold, statistical sampling and I think the two major things on the end; there really were no preapproval inspections or postapproval inspections and certainly the CDER versus the district responsibility was somewhat unclear because, again, all approvals came through CDER with the district not having the wherewithal to really do a lot of inspections at that time.

[Slide.]

As a result, certainly there was a stop put on so, at the beginning of this whole scenario, was to solve and

resolve those issues. Certainly, with manufacturing formulation changes, is to assure that if, in fact, you are going to manufacturer a batch at the site you intend to market, with similar equipment, then that certainly would be able to give some assurance that we are not running into any difficulties in relative stability and/or bioavailablilty.

Thus, the beginning of the site-specific stability which started back in 1990. However, we must admit that, since then, we have come a very, very long way.

[Slide.]

What has occurred since then? Since then, the minimum batch size, the unit size has been established or 10 percent of the manufacturing batch. Certainly, process validation that has been ongoing. Meetings have been held and now, in the new GMP guidelines, whenever they will get published, also addresses validation to a great extent.

We now have to have first-reproduction batches prior to approval or prior to marketing after approval and prior to marketing. We are all subject to preapproval inspections to validate and verify that, indeed, the manufacturing equipment hasn't change, the formulation hasn't changed.

So all these are in place right now to assure that, indeed, the major changes that could affect, potentially, the product are, indeed, under control. And

then, of course, you have SUPAC and BACPAC guidances. SUPAC very much addresses site changes.

[Slide.]

Other guidances through ICH, packaging and stability guidances and, certainly, the FDAMA Act which is bringing on more guidances to assure that we, indeed, do have a quality product.

[Slide.]

Just to address, again, what are the issues we are trying to address. Certainly, it is with the agency and FDAMA and the Paper Reduction Act, it is really intended for us to try to decrease the amount of regulatory burden and still assure the quality of the product.

I propose to you that I think this really has been established and so, therefore, these ideas that have been an issue in the past are being addressed now.

First of all, small batch sizes is being addressed now by having minimum batch size or 10 percent batch size. No process validation. In most cases, almost everyone has somewhat process validation of submission batches. Certainly, the requirement is that you have to validate the three production batches postapproval prior to marketing which, again, can and often is reviewed by the district to assure that the product meets all specifications, to assure it meets all the quality parameters that have been

established.

Changes in site is addressed by SUPAC. We are allowed, right now, to make site changes under certain guidances. Changes in manufacturing and formulation. Those are the big issues because, this morning, I have listened to some speakers. When some of these--Dr. Seever's presentation came up this morning, I am questioning whether or not some of these include manufacturing and formulation changes.

Quite often, old historic data will include that. We know that this will affect the product. But, under conditions when you have no procedure change, when you have no formulation change, when you are within the guidance, even SUPAC will tell you that it is perfectly legal and allowable to make a change, a change being an affective change, under many conditions.

We have this in place. It is being worked up on and followed. There shouldn't be any difference between whether or not it is a current product. As was said, the drug entity doesn't really have a memory. They don't know whether it is a marketed product or whether it not it is a new product.

[Slide.]

Again, bulk hold, statistical sampling; certainly, review of information. One of the issues is do we have

enough information, are we doing what we are supposed to do, are we doing what is being promised to do. Of course. The district has a right and does come in for preapproval inspections and postapproval inspections and is able to review all the information and data.

They have the NDA. They have to see what the production capabilities are. Again, is there an issue between CDER and the district? The only issue here, if there is one, is really what is GMP and what, really, is a CDER issue and/or a submission issue for preapproval.

That, I think, really sometimes becomes a very hazy--and it is not a very defined line. I submit to you that if we have, with all these things, these guidelines in place, with all the issues, that the initial intent of what site-specific stability is to do has been addressed along the way with many different guidances.

[Slide.]

So, really, as a conclusion, we would recommend for the FDA to reevaluate the position on site-specific stability. I submit to you that many GMP issues which are really the same examples given are really GMP and not really submission issues, that industry is pretty well doing what it is required to do.

SUPAC guidance assures that things are being followed in a regulatory perspective. Therefore, I would

certainly submit that site-specific stability should not be a requirement for any regulatory submission batches.

Thank you.

DR. WILLIAMS: Tony, thank you very much. Our next speaker is Dr. Patricia Tway of Merck and Company who has ten minutes.

I might say, people have been relatively brief so we have a little extra time. So nobody needs to feel too rushed.

DR. TWAY: Thank you very much.

[Slide.]

I do appreciate the opportunity to be here and I thank you very much. Merck has spent a great deal of time thinking and talking about site stability over the last two or three years. The theme that I am going to bring to you today is not a new theme. It is the same story that we have been hearing all morning, that we honestly do not believe that stability is the correct marker of whether you can successfully scale-up or you can transfer or whether you can validate a process.

We spend a great deal of time on product development, on scale and on the transfer issues but we just do not honestly believe that stability is the measure that one should use in order to evaluate it.

Since we honestly do not believe that, we also

have found, in reviewing and trying to develop how can we do site stability, that it has a tremendous impact on our developmental time line which I will share with you.

It impacts our ability to file, which then means that it impacts our ability to get the product to the patient and it also has a financial impact.

[Slide.]

The FDA proposal, which we have reviewed briefly, the new one, basically focusses on three-months accelerated stability and, obviously, the beginning of a long-term study on drug product made at the final manufacturing site--with the emphasis on site here--preferably with drug substance also made from its final manufacturing site.

This does not necessarily have to be at full scale. It does not necessarily have to be in commercial equipment. So, again, we do not--in some of the examples that were given this morning in the presentation from the FDA, while we can't determine the root cause of the stability failures, some of them appeared to be more process changes that could occur on the same site as you scaled up or even as you changed equipment at commercial scale.

[Slide.]

Basically, we honestly believe that the only way one can do develop scale-up and then transfer is to accomplish all of the items and to address all of items that

are in the outside circles, starting, obviously, with environment which we have spent a lot of time talking about this morning.

If your material is sensitive to humidity, you need to know that through development and then you take the appropriate actions as you do scale up and transfer. Covering CGMP, SOPs. All of these have been mentioned earlier today. The technical staff, raw materials, how we test them, what methods we use. None of these are site-specific from a global industry such as Merck.

The same tests will be used, the same vendors are used, no matter where we are going to making the manufacture.

Looking at process parameters, and we can just continue on around. I don't want to do that. We have talked about them earlier today.

[Slide.]

If you look at stability, however, on the other hand, stability is integral to the drug product and to the drug substance. Basically, the molecule that we choose to develop has an inherent stability. It is a thermodynamic stability. Obviously, we choose it carefully.

We then, if it is not--and I will give you some examples in the next slides of molecules that are not necessarily inherently stable--we develop the manufacturing

process looking at crystal form or polymorphism, the tendency to develop polymorphs, whether one needs to control particle size.

All of this work is done during development. Any and all of these things could affect stability. But if the work is done appropriately through development and that work is generally explained, described in the NDA, then that is the basis for allowing us to scale up to transfer to a different site and to do full-scale manufacturer.

[Slide.]

This is some data which our lawyers did let us show. Basically, since 1992, Merck has filed thirteen NDAs, gotten approval. These are thirteen new chemical entities, NDAs. We have launched those products. Basically, these are not the six most stable. The others look the same. I just wanted to fit everything on one slide. Some of these actually are not inherently stable.

What we see is, if you look at crixivan, we have a variety of dosage forms here. Crixivan is a capsule. We use a roller-compacted powder into the capsule. Cozaar is a direct compression. Tim. XE is a ophthalmic solution. Aggrastat is a sterile injection.

Singulair is a wet granulation. In the case of singulair, or monolucas which is the API, it is very sensitive to humidity. You put it out on a nice warm day,

it will become a puddle on your table in no time. Crixivan, or indinavir sulfate, also has tremendous sensitivity to humidity.

These things were developed--we determined how to handle it no matter which site we are making it at and that was built in to the process development and the process scale-up and transfer.

On the left-hand side of the screen are the market-container stability data, three batches. The right-hand side are three batch-production data. These were our validation batches which, if they had failed stability, you would have known about because we would have had to come and recall them from the market.

I gave you the furthest time point we have out. In some cases, it is 24 months. In others, the studies are only out to 12 and 18 months. In all cases, the stability profiles are absolutely identical and, in none of these cases, were the market-stability lots made at the same site as the production batches.

In many cases, they were not even ever made in the same state and some of this work was obviously done in Puerto Rico where there is a sensitivity because of the temperature.

We have looked at all of the other products and, in no case, have we seen systematically a change in the

stability profile as we have transferred a product from one site to another.

[Slide.]

While we truly do not believe that the stability requirements add value, they do impact our ability as an industry to get product on the market. There is a financial impact and there is a timing impact.

[Slide.]

This is a typical developmental time line. It is an example. There is probably no single product that you do exactly this way, but if you look at the time line, basically, this was before site-stability requirements where we essentially and frequently need to build facilities in order to manufacture for commercial availability.

The decision of where we were going to make the API and the start of the construction occurred post the beginning of phase III. We knew, essentially, we had a product. We have only had one product in the last 30 years that got into phase III and failed. So if we get into phase III, we are very highly confident we are going to have something to file.

If you use this time line which, then, essentially, allows us to be making our validation lots and doing validation just about the time of NDA filing and you overlay on that when we would have stability, the stability

data from those batches become available about nine months post filing. There really is no way we could accelerate that unless we use the next time line.

[Slide.]

The next time line is based on what we would have to do if we were going to have stability data for the same product at the time we file the NDA. Basically, we would have to, in many cases, make a decision that we were going to commit large amounts of capital and go into construction for the API site somewhere between nine and twelve months before we went into phase III, before we knew whether the product was efficacious enough to merit further development, certainly well before we knew any idea, really, of what the dose was going to be.

The capital that would be at risk at that point, in those nine to twelve months, is somewhere between $10 million and $20 million. This is not capital that industry lightly cares to commit until they really know they have a product.

The only other option we would have would be to delay construction and then to delay the filing which means our clinical program would be finished. We would go ahead and file internationally but we would not be able to file in the U.S. because we would not have the appropriate stability data.

[Slide.]

So, as an alternative, because we do recognize that there is a desire on the part of the agency to have data that shows that we can scale up and we can transfer-- the data that we feel is appropriate, really, would be shown here that three months before the PDUFA data, we would provide the data on three batches of the API, three batches of the drug product made from that API.

We would also provide a summary of a validation report. As others have mentioned, the validation protocols are rigorously reviewed by the field. They go through them very, very carefully during PAI. But, if desired, we could provide a summary of the validation report. This would be on material made at the final site, at full scale and in the final manufacturing equipment.

We believe it should address, and be a better marker of, what we are trying to measure here than stability.

Thank you.

DR. WILLIAMS: Pat, thank you very much.

Our next speaker is Dr. Massa from Lilly who also has ten minutes.

DR. MASSA: Good morning. One of the neat things about being late in the program is that, as somebody mentioned before, a lot of folks have said a lot of the same

things you are going to say. So, in the interest of time and making a little more time for questions, I am only going to present two of the slides that I had intended to use and try and address a couple of comments to the revised proposal.

[Slide.]

One of the comments, I think that Bob made earlier, is that there is concern that things might not be quite the same at the commercial site as they are at the site where the R&D batches were made and that site-specific stability was needed to determine whether or not anything in that facility may cause a stability problem.

One of the things that is inconsistent with that comment is the provision in the 1998 guidance that says where there is a pilot plant on the intended commercial site that data from batches made in that pilot plant would suffice to meet the site-stability requirement.

Clearly, some of the issues that Bob addressed would not be addressed by this particular provision. So, again, I am kind of wondering what is it that we are trying to do when we ask for site-specific data. Are we validating a geographic area or a zip code or are we, indeed, validating or getting additional information on commercial production equipment.

[Slide.]

Somebody made a comment before that their recommendation was to adapt the language that is in Q1A and that is in the revised Q1A and not to implement this until this discussion has been had at ICH and the other health authorities have been able to input into this process.

I think it is important to note that no other health authority requires site-specific stability data. I guess this is really a challenge to FDA. If you think your case is that strong and you can convince the other two regions that this is a necessary requirement, I think industry would be responding very differently to the request for site-specific data.

I would like to spend just a couple of minutes talking about the revised proposal. I agree with my colleagues who have spoken before that we really haven't had enough time to look at this in depth. But I am glad to see that FDA is at least willing to make revisions to their policy. I think this is a good thing. I think we are also talking more about this.

I don't think we have done enough of that to date. It is good to see that our request to see examples of what the issues are have come forward. I think we need to continue those discussions to get to root-cause analysis and separate out the things that are truly stability issues as opposed to GMP and facility-qualification issues because, if

that is case, then we need to do things differently as we do our facility qualification to address some of the issues that Bob has raised in his examples.

I think this is a good basis for discussion. The categorization into major and minor potential to impact the product requires submission of site-specific data, site-specific stability data, either at submission of the application or in the midpoint of the review cycle. In either case, much like my other colleagues, I still don't see this as a necessary requirement and, at least for now, I see this as scientifically unjustified

If we have further discussion and it can be shown that there is a scientific basis for this, maybe that opinion will change. Again, I would reiterate that no other major health authority requires site-specific stability data.

On the question of drug substance, FDA notes that one major potential for adverse effect related to site transfer is a drug substance whose polymorphic form or particle size is critical to performance of drug product.

I would ask, what is the basis for this. I had the opportunity to discuss this with my development colleagues at Lilly. I no longer consider myself a scientist. I gave that up when I became a regulatory guy, so I went to the scientists to get the answer.

They uniformly stated that a change in polymorphic form as well as any of the other physical characteristics that FDA was citing as being related to a site change would be caught at release testing and it would be very rare for any of these to be caught during stability during independent of release.

Furthermore, this is inconsistent with the 1998 draft guidance on stability. In discussing stability testing of postapproval changes in the manufacturing process of a drug substance, FDA stated, and I am quoting page 87, lines 2770 to 2773; "Because chemical stability is an intrinsic property, changes made in the preparation of that substance should not affect its stability provided the isolated substance remains of comparable quality for attributes such as particle size distribution, polymorphic form and purity profile, and other physical, chemical properties.

In other words, and FDA can correct me if I am interpreting this improperly, if a sponsor demonstrates that drug substance, previously demonstrated to be stable, is shown to be comparable based on quality attributes at release in the face of a manufacturing method change, stability is not required to obtain approval or show that the product is comparable.

This assumes that a standard stability commitment

will be included in the application. If that can be said of a manufacturing change to a drug substance, it should apply to a site change as well. Therefore, release data from tech-transfer lots should suffice to demonstrate that site transfer has been completed successfully and site-specific stability data should not be a requirement for approval.

Lastly, I would like to address one issue related to drug product and one that we have not been able to figure out and certainly welcome discussion with FDA on the issue. The revised proposal states that site transfer for a sterile lyophilized powder would be in the major category while a non-sterile solution or powder for oral solution or suspension would be in the minor category.

According to the table, for the first example, we would have to submit the data at the time of submission. For the other, we would only have to have a stability commitment submitted to annual reports. And I guess we would have to ask, what is the difference from a stability perspective, other than sterility, that differentiates a non-sterile from a sterile powder and how does this impact site transfer.

We agree, and FDA, I'm sure, would agree with us, that the environment in which we make a sterile product is absolutely critical. But we also go through sterile process validation and part of site transfer for these products is

submission of sterility assurance and sterile process validation.

Sterility, itself, in our minds, is not a stability issue. It would be very rare for a product to fail sterility on routine stability that has shown to be sterile at release. We agree that site transfer of a sterile product is critical and does require sterile process validation. However, we don't see how the issue relates to stability.

So those are just a few comments. Certainly, we will give you more. In closing, I think, finally, we have seen some data. I think that is what we been asking for for the last two years. Now it is a matter of finishing that and getting to root-cause analysis.

DR. WILLIAMS: Toby, thank you very much.

Our next speaker is Gary Dukes speaking for Pharmacia Upjohn.

DR. DUKES: Thanks for the opportunity. II am presenting Pharmacia and Upjohn. We support the PhRMA position in opposition to the requirement for site-specific stability.

[Slide.]

I would like to explore with you why I believe that a site-specific stability requirement is an answer in search of a question. Where does site-specific stability

add value? There are three areas where this question could arise.

How well do we understand the stability performance of the product and the drug substance, how well do we understand the process performance of the product, and how well do we design and execute the technology-transfer scaleup and process validation for the product.

[Slide.]

What would site-specific stability add to the existing stability performance profile of a product. Now, a stability performance profile consists of the data shown here, from stress stability studies to the stability of the clinical batches, the identification of the degradation products and qualification of them in the product, the supportive stability studies and, finally, the primary stability studies, twelve months of long-term data and six months of accelerated data.

[Slide.]

This stability performance profile is used to determine the specifications and release limits for the product and the API. It is to predict the packaging and storage conditions and the initial expiration dating period for the product. Three months of site-specific stability would not add any meaningful knowledge to the stability performance profile for the product.

[Slide.]

What would site-specific stability add to the process performance profile of a product? The process performance profile of a product is a continuum of knowledge gained from the process development and validation, from the laboratory scale batches through the pilot plant to full-scale manufacturing.

[Slide.]

This continuum of development activity is identified as the equipment and conditions necessary for a robust process. It identifies the critical quality attributes of the process and the critical process parameters necessary to achieve these critical quality attributes.

The process performance profile forms the basis for scaleup and technology transfer plans and the process validation protocol. Three-month site stability does not add knowledge to the process performance profile.

[Slide.]

What would site-specific stability add to the quality of the product from the manufacturing site? As Scott Reynolds said, the facilities and equipment and SOPs and utilities and that sort of thing are GMP issues. Environmental and in-process controls specifications are derived from the stability performance profile and the

process performance profile.

The validation protocol demonstrates the reproducibility of the process and equivalence of the product on scale-up. The success of scale-up and technology transfer are judged by the consistency of the quality attributes for full-scale and validation batches, not by site-specific stability.

[Slide.]

There is stability at the final manufacturing site. By the commitment submitted in the application, the firm is obligated to place the first three full-scale batches on stability at both accelerated and long-term conditions. The performance of the product produced at the final manufacturing site is not just an agency risk. It is a shared risk.

That is because the marketplace is fiercely competitive with therapeutic and generic substitution widespread. One needs only to log on to drugstore.com on the Internet to see an example of that reality.

So it is contrary to our firm's best interest to risk launching a new product only to have to recall it due to inconsistent stability performance.

[Slide.]

In summary, development of the stability performance profile and the process performance profile for

a product is a cumulative process during drug development which results in a thorough understanding of product stability, a thorough understanding of the process.

[Slide.]

Site-specific stability does not add value to either of these topics. The success of technology transfer and scale-up relies on the knowledge gained in the stability performance profile and the process performance profile and the demonstration of process robustness through process validation in the final manufacturing plant.

Site-specific stability does not add value to or insure the success of technology transfer, scale-up or process validation.

So I come back to my original contention. A site-specific stability requirement is an answer in search of a question and there is no question.

DR. WILLIAMS: Gary, thank you very much.

Our next speaker is Taylor Burtis from Genentech.

DR. BURTIS: I would like to thank the forum for presenting this chance for Genentech to speak.

[Slide.]

From a different perspective, from a biotech company, Genentech is recombinant therapeutics. We have a different slant on some of the stability information that is presented in the stability guidance. I would just like to

take a second to step back a little bit and look at the overall guidance.

[Slide.]

These are just sharing some of the recommendations that we made to the docket number during the comment period. The current guidance that has been drafted is more appropriate for stability of a small-molecule pharmaceutical or where a characterization of lot release is not adequate to support equivalence.

We also felt, from reading this guidance, that we really would prefer that a separate guidance document be written for recombinant therapeutics. Now knowing that we would like to, after this statement, also say if one size could fit all, we would appreciate that we make sure that there is some flexibility and adjustment in the guidance document.

We culled out seven specific sections of this draft guidance document that needed to be reevaluated and inclusive of recombinant technology.

[Slide.]

Things change rapidly. When we received the E-mail on Monday, with the attachment of the new site-specific draft section, we reacted. One of the things that I was given the mission to do was to go out an slay the dogma dragon that accelerated data is not appropriate for

recombinant therapeutics or for proteins.

I am so glad to see that, in trans-flight on Tuesday flying out here, that the footnote to the table has been removed. Thank you very much. I can go back and say, "Listen; they really heard us and they removed this footnote," for the exception for biologics not having to submit accelerated data.

We really believe, and this is something, again, just to give information why Genentech feels that accelerated data is appropriate, we actually feel it is very valuable in assessing the process-related changes, not site-specific but process-related changes.

The accelerated data or the degradation profile that we see during our research and development process is what helps us fix the actual manufacturing schematic that we are going to be using, no matter what site we are at.

Another thing is we also use it for looking at overall data that we would have after one month. We find that we have appropriate data after a one-month period. It does not take us three to six months of accelerated data time points to see how this protein is going to react.

[Slide.]

So our recommendation for accelerated data is that the time interval that is set in the guidance document be not arbitrarily set but looking more, going back into the

research and development and the characterization of that protein or that molecule, whether it is a small molecule or a recombinant therapeutic, is that you look at the data that has been presented during the development process and then base your accelerated data time points on that.

One month is sufficient for Genentech's experience. Two to three months would definitely be too long. We also recommend that accelerated data be submitted for site-specific change. We only require that one batch be submitted.

If additional needs to be submitted later on as part of postapproval commitment, that is something that we would negotiate and consider, but we think, for the approval process, based on the profile that we would see with one month worth of data, we could judge and predict how that therapeutic would perform on the end of the stability profile.

[Slide.]

Going off for real-time information for a well-characterized molecule, and based on all the other speakers that have presented, this is given that all your quality controls, all your validation, all your specifications are being met. These are things that are not changing in moving to a new site.

We have had, in our experience, and we have had

some very complex site changes--we have not seen any site change affecting the stability profile of any of our products, either in development or in the market.

We recommend that, for approval, we submit four to six months of real-time SS data. We feel that this would be sufficient. Again, we would talk with the agency and consider if there needs to be postapproval commitment. The reason for the four to six-month time line is a lot of our product, we are going to be probably going in under fast-track. If we had to hold up for getting a twelve-month period of stability data, then that would delay us to market.

[Slide.]

Again, this is from the recombinant therapeutic perspective. This is what we would like to see. This is what we have--if site-specific data is going to be required for stability, this is what we would like to see if it going to be mandated and that is one month accelerated data on one batch to be provided in the submission and then, during the four to six-month review period, that we would provide one batch, again, of data for the time periods for real-time data for stability.

Again, thank you very much.

DR. WILLIAMS: Taylor, thank you very much.

Our final speaker for this section of the morning

is Robin Roman who is speaking on behalf of SmithKline Beecham.

DR. ROMAN: Good morning. Thank you very much.

[Slide.]

This is probably the most unenviable position on the program. I have very little to say that has not been already said and I am also holding you up from having lunch. But I will try to put a slightly different perspective on some of the things you have already heard.

I am actually going to focus, if you look at site-specific stability, on the analytical issues. In my talk about analytical issues, really, I am referring to two of them. One is the analytical method transfer and the second is the use of stability data in setting specifications.

[Slide.]

Rather interestingly, we have heard a lot about process validation and process transfer today. But no one has actually mentioned the fact that there is another very important component to this which is the transfer of the analytical methods.

I am speaking for SmithKline Beecham, but it is certainly based on meetings I have attended in other symposia. I think it is pretty well common in the industry that there actually is a formal protocol-driven transfer of analytical methods that takes place from the developing

site, and I am speaking from an R&D perspective, to our commercial site with well-defined criteria for success.

Clearly, this is a GMP aspect to make sure that the commercial site has the quality-control capability to perform the methods, but the driving force for doing this is what I call "good business practices." It is in our interest to make sure that the commercial sites can actually perform these methods, release batches appropriately.

I am hesitant to say this, but it is rather interesting that the industry has been able to do this and develop a reasonably standardized protocol in absence of any guidelines from the agency. So, Eric, a new opportunity for you.

[Slide.]

The second aspect of the analytical methodology is talking about specifications. A number of people have actually talked about this and I won't dwell in detail on this. But, certainly, from an NCE perspective, the specifications are developed primarily from the three batches of primary stability data that are set in with the whole backlog of data that has come from different kinds of different clinical supplies

That is the basis for setting the specifications. I think that all of us realize that the specifications that are set at this point are only conditional. We are only

talking about three batches of data and, very often, we are talking about data which is not made in the commercial factory and not made at commercial scale.

But we use that data to set the specifications.

[Slide.]

What I would like to do, then, is, with that basic background, is, without worrying about the site-specific stability proposal from the FDA, to look at what we get at when we actually do the stability testing of the first three commercial batches.

We have methods and specifications, at least conditional specifications that are approved by the FDA. What we do is we actually repeat the same stability protocol on those three commercial batches that we used on the three that were filed with the NDA.

If we remember that, again, the reason for doing stability is, really, only twofold; to help us set specifications and to establish a shelf life and storage conditions for the product. So the way that we actually establish that shelf life and storage conditions for the product is based on room temperature data or the storage data for the product.

So it is really only the 25/60 data that we are actually using from the data submitted in the NDA to establish this provisional shelf life.

What we then do is we take this parallel series of experiments--again, three experiments done with the same protocol, produced at full commercial scale in the factory, and we repeat that. At the end of a year, we can go back. We can do regression analysis. We can do statistical analysis on that data in the factory.

We can compare it to the data submitted. We can have a good statistical justification that the product in the factory is the same as, better than, or worse than the initial data submitted and we can adjust the shelf-life accordingly. To me, that is good science. That is a sound way of doing it.

The difficulty I have with the FDA proposal, particularly when we are looking at one batch, short-term data which is actually not used to establish the shelf life--accelerated data isn't used to do that--what do we do with that data?

It is not clear to me if we have data in the NDA that says, at the end of three months, we have 0.2 percent degradation. If we get data from the accelerated data that says it is 0.1, is the commercial batch twice as good? If it is 0.3, is it 50 percent worse?

I have a hard time doing that. For me, at least, it is trying to come to grips with what we get with that information and how we make a judgment on it that I am

having trouble with.

[Slide.]

Good science? Good regulation? I believe that. I know a number of my colleagues here from the FDA, we have had scientific discussions before. The FDA has got a strong scientific tradition. I think that has led us, in many cases, to very good science-based regulations. I think the BACPAC 1 example is a good example of this.

But I think you are hearing, in a variety of different ways, from the industry that the site-specific data doesn't seem to be in that same category. We have seen some new data today that I hadn't seen before, some new examples. There may be cases where, in fact, this is justified.

But it isn't clear to me, and even the new proposal that has been presented, this same problem that I am having, preparing one batch of short-term data to a whole body of stability data--I don't think that is a terribly valuable thing to do.

[Slide.]

So my proposal, which is, in fact, a variation of many others that have been here, is that we really have to discuss this more. There are a number of fora that have been suggested for discussing this. I suggested one here; the ICH Q1A has stated again. Site-specific stability data

is a topic on that agenda, but that isn't the only way to do it.

Clearly, there is a fundamental disagreement on the science, at least from the positions that have been presented and I think we have to narrow that position.

Thank you.

DR. WILLIAMS: Robin, thank you very much.

I would like to thank all of the presenters at the open public hearing for being concise. The reward for that, now, is that we have a little bit longer for lunch. As you all look at your agenda, we really didn't want to take much of a break at all for lunch, just twenty minutes. But, now, I think we have forty minutes.

So, if nobody objects, I will close this part of the meeting and will see you again at twenty minutes after twelve. I would like to remind everybody who wants to speak further this afternoon that they do need to register with Kimberly, the way it is described in the packet.

[Whereupon, at 11:40 a.m., the proceedings were recessed to be resumed at 12:20 p.m.]

AFTERNOON PROCEEDINGS

[12:25 p.m.]

Discussion

DR. WILLIAMS: Thank you for coming back in a timely way, as they say.

In this section of the program, we have an opportunity for people from the public to speak at the microphone if they wish. We did ask for people to sign in and give us some information but, in any case, anybody can speak if they wish to come and make a presentation.

If they do so, we would like a card or something about who you are and what you representing so we can get that information into the transcript.

We did have some indication from people who wanted to speak so, while people are out there wondering if they want to speak or not, I will start on some of these names. We had a request from Dennis Weichel from Abbott Laboratories. Is Dennis here?

DR. WEICHEL: I'm here, but I didn't really care to make a request. Most of the points I was going to make have already been made.

DR. WILLIAMS: Thank you, Dennis.

Our next requester was Ajaz Hussein? Ajaz, you didn't want to?

We had somebody--John, I want to say Witte--from

Novartis. Did you want to speak further, or did you get your opportunity? He's not here? Rebecca Devine, did you want to speak?

DR. DEVINE: I think what happened was some people signed on the wrong--

DR. WILLIAMS: That's what I think, too.

Let me ask, does anybody want to come forward now and make a public comment? We will skip the last. Dr. Massa?

DR. MASSA: Two things I wanted to say. First of all, in response to a comment that Bob Seevers made about failed stability batches, I don't think that those batches, necessarily, get buried along with the body.

I know in my previous lifetime, as well as at Eli Lilly, we do investigations on why those batches fail and they become part of the development report.

DR. SEEVERS: I agree, Toby. What I was saying-

DR. MASSA: That may not be the case all over, but I just want that clear.

DR. SEEVERS: In fact, I expected that. What I was trying to say was that the agency, as a rule, does not see those data. Sometimes, during a preapproval inspection, an inspector may run into those data. But, at the center, we generally don't get those data.

DR. MASSA: I think that is an issue that,

probably, at some point, needs to be discussed because we consider the field, as well as the center, the agency.

DR. SEEVERS: Absolutely.

DR. MASSA: If there needs to be better communication between the field and the center, in terms of requests for looking at data and having data sent back, let's do that. But let's not create--I think what we don't want to do is create an extra hurdle because they are not fixing the problem that needs to be fixed.

DR. SEEVERS: I want to respond to that because I don't think is a communications problem between the field and the center, at all. We had not specifically, until the last couple of years, sought to address the question of where are the data. We have been working with the field on this and several of the examples that I showed came from that collaboration.

So that communication is working.

DR. MASSA: Okay. Good.

Roger, I would like to change my affiliation hat here from Eli Lilly to the Biology and Biotechnology Committee of PhRMA. B&B of PhRMA is not in agreement with the Genentech recommendation for submission of site-specific data, particularly for well-characterized products.

I think we have been on record for a number of years indicating that a well-characterized product should

be--and I think this is also consistent with FDAMA--that these products should be regulated as closely as possible, as are drugs. So we don't see that there needs to be a separate guidance there. We are referring specifically to well-characterized products.

DR. WILLIAMS: Toby, if I may ask, what is your position on the need for additional site-specific data?

DR. MASSA: Obviously, wearing either my Lilly hat or my PhRMA hat, we don't necessarily agree that we need site-specific data. I think, for well-characterized products, there shouldn't be any difference between a well-characterized biologic and a small molecule, but that needs to be a case-by-case discussion between the sponsor and the center, be it a biologic that is regulated in the Center for Drugs or in the Center for Biologics.

DR. WILLIAMS: Thank you.

Any more comments from the public? Yes, sir? Please come to the microphone and identify yourself. If you have a card, we would appreciate it for the transcript.

MS. WYVRATT: I am Jean Wyvratt from Merck. I would actually like to actually provide some industry clarification to a comment that Dr. Seevers made wher he was elucidating the examples. It is regarding the request that is sometimes made to wait until we have "X" number of batches at the commercial site before we finalize the

specifications.

I just wanted to clarify that, in many instances, what we are looking at here are impurity specifications. We are looking at differences of a tenth of a percent between what we would finalize at and what we initially have as the specifications that have come out of the development process and the initial three commercial validation lots.

Where we would finalize the specifications at is always well within the experience as well as the qualified safe level of those particular quality attributes. What we are looking at, really, is to get a larger database that allows us to finalize specs.

At Merck, for example, in recent evaluations of this type, we have probably gone 50/50 different ways. Some of it has been tightening by a minor amount. Some of it has been broadening by a minor amount.

But we are not really talking about major significant changes in specifications in this finalization. It is not a site-specific issue.

DR. SEEVERS: I think it is in that what we heard from industry in this morning presentation is that technology and transfer and process validation produces a gold-plated, perfect, sure-fire product. Yet, on the other hand, there are regularly cases such as, as you and I have described, where it is necessary, and the agency

acknowledges that it is necessary, to get more experience at a particular site at that scale before finalizing specifications.

So you can't have it both ways. Either it is gold-plated perfect and we don't have to worry about it, in which case the specifications should be set during the review process, or there is still a little bit of learning to go on and it is not a guarantee. If it is not a guarantee, then site-specific stability does add value.

MS. WYVRATT: What we are getting at, though, is that, really, what you are doing is an expanded dataset. You have "X" amount when you finish development. You could go on and generate more within the development context and most likely come up with the same conclusion.

But, in the sense of, at the production site that we are now at, continuing to build the "N," the number of lots that you have to allow you to, hopefully, tighten because your process is lining out, the more you do it. That is really what we are dealing with.

It is not looked at within the industry as a site-specific issue is what I am trying to get at.

DR. REYNOLDS: I wonder if I could comment on that as well.

DR. WILLIAMS: Jean, thank you very much. You are certainly welcome to say at the microphone, if you would

like.

DR. REYNOLDS: I think, just to continue on with that issue, I think the objective should be to make sure that the process development and process validation establish a range within which the process will deliver, whether it is with regard to product specifications or in process controls.

That certainly has to be within the limits that were already established as necessary to assure safety and efficacy of the product. So you have the outer ranges for safety and efficacy of the product from the quality standpoint. You have the range within which the process validation will be executed.

From a good business standpoint, and just good regulatory controls, as process capability is developed, it is certainly reasonable to expect that we will set specifications. We will further tighten that range. I think that is the situation that you typically see.

I don't think it is an issue of the initial process validation not being satisfactory to provide good quality product. It is the subsequent desire to have that tightened down and really control around the absolute process capability that can only be achieved during multiple batches just from a pure statistics.

So I think it is a little different from simply

saying you need to change it after you have run many batches.

DR. SEEVERS: I would agree with you. It is not that you need to change it but that process validation is not a sure thing. That is the message that I am trying to get across.

DR. REYNOLDS: I think process validation is a sure thing to provide a safe and efficacious product and a robust manufacturing process. If you would like to provide additional and tighter specifications around that process, based on extended manufacturing experience, then that can be done, but it doesn't mean that the initial validation exercise didn't provide a robust and reproducible manufacturing process.

It simply means you established a broad set of ranges, or a broader set of ranges, than you might be able to establish after an extraordinarily long period of time and experience in manufacturing.

But it doesn't imply that the initial exercise did not deliver a robust manufacturing process to produce a product that has an acceptable quality of safety.

MR. LACHMAN: I would expect that the conditions of approval would be the specifications that were filed and which resulted in the specifications based on the three process-validation batches.

Now, with experience, you may be able to determine whether dose specifications can be met or they need to be tightened or loosened. But I think the conditions of approval are the specification that you submit your NDA. So I don't know, from a compliance point of view, if you can have dynamic specifications. You can modify them with supplements later on.

DR. SEEVERS: That is the process we are describing. A firm will commit, after a certain number of batches--ten or twenty is typical--submit a prior approval supplement to tighten specifications, if warranted. Or change them.

DR. MASSA: That is also consistent with what is being proposed in Q6A and B, that you go in and not necessarily set supertight specifications to what would appear to be the capability of the process based on those three lots. And you would come back in after some period of time and set either a wide spec or, as long as it is qualified, by tox or clinical data, or a tighter spec if you showed that the manufacturing process has better capability.

I can think of an example from a previous lifetime where we had very limited data on extractables from the last components. When we expanded the number of lots from these elastomeric components, we found that these extractable levels were higher than had been in the initial submission.

So we had to go back in and modify that specification.

So I think that is certainly consistent with what has been proposed in ICH. Eric, correct me if I am wrong. Is that not the process?

MR. SHEININ: That is the process. I guess what you are hearing from the FDA perspective is if you don't have enough data to support a final specification, then that seems to justify having some site-specific stability as well. I think we should go on from here.

DR. WILLIAMS: Further questions or comments?

DR. CLARK: My name is Bob Clark. I am from Novartis. I wanted to switch the discussion over a little bit to postapproval changes. I have been successfully making postapproval changes for a number of years to a number of products. One of the regulations that I have employed is the 314.70(c)--I think it is (3). It is the last one of the change being affected, regulations whereby you are allowed to change the site of manufacture of your drug substance provided that the facility you are changing over has an acceptable inspection for the type of process you are using.

I was wondering if site-specific stability would add a further constriction or restriction on that particular regulation.

DR. SEEVERS: No more than SUPAC already does.

And SUPAC is a lesser regulation. Remember, and this is what has been confusing to the agency, in SUPAC, the concept of site-specific stability was agreed to with industry and the need for it was agreed to.

With a new drug which has not been manufactured before, above a pilot scale, there is, by definition, less information, less experience. What we are hearing from industry is that site-specific stability is not needed there. And there is a dichotomy which is confusing.

DR. CLARK: We haven't seen BACPAC 2 yet, so we don't know exactly all the provisions that it is going to encompass.

DR. SEEVERS: What we do today and in the next few months will affect BACPAC.

DR. BYRN: This is more a question for the agency. But drugs that are life-saving drugs, AIDS drugs and rapid-approval drugs, what are the regulations for those. Do those shed any light--in other words, how much validation has to be done and then how much site-specific stability has to be done for those drugs? Do we know? Do we have that?

MR. SHEININ: There are no regulations that deal with site-specific stability. It is in our guidances, our guidelines. I guess the process validation and the first reproduction batch part is GMP regulations as to when those have to be done.

I know certainly for orphan drugs, which some of those products could fall into, and we have said for products for pediatric use, there has been concern about the need to do process validation on three batches, especially for a product where you are only going to make one batch a year. Those batches would be thrown away because there is not a market for it and compliance has said those can be done sequentially.

They would allow a batch-by-batch release after the process validation. So it depends on, I guess, really not so much what its intended use is but what the market is. If it is something that would qualify as an orphan drug or less, then there are some provisions that compliance has said they would go along with to allow that not to have to be done up front.

DR. WILLIAMS: Steve, if I may add, I think in our draft sort of concept paper, we do allow the fact that medical need could adjust the request for site-specific data.

DR. ROY: Suva Roy, Glaxo Wellcome. Bob, you said something about the SUPAC requiring site-specific. But for SUPAC, for postapproval changes, the product is already at the site. So all the change are done at the site. So it is no different. So the data that is generated is site-- because the product is there.

So you cannot equate a product that is not yet approved to a product which has been approved and is at the site.

DR. SEEVERS: That is what we just said.

DR. ROY: So you cannot equate it. I think what I am hearing is that you are saying that you can do it for SUPACs. Why can't you do it for new drugs? Is that correct?

DR. SEEVERS: That is the question that I raised. Better yet, why can't you do it? I am not talking about capabilities but necessity. Why is it not necessary for new drugs when it was understood that it would be necessary for changing the manufacturing site postapproval for an approved drug?

DR. ROY: I think I am going to put on my old FDA had and SUPAC IR hat. The whole reason for that was because, again, what I said, the product is already at the site. So you don't do the changes at a different site and bring it to the site. What changes that happen, in most cases, are at the product manufacturing site.

So the data that is available is automatically site-specific.

DR. WILLIAMS: Suva, let me add a clarification, and Bob, check me, but I think what we are saying is--for example, SUPAC MR says that if you change a site, you do a

bioequivalence study for a modified-release dose form. Now, that is actually far in excess of what we are suggesting here for site-specific stability.

But I think, if I could argue Bob's case, we are arguing that there is a motivation for some additional information in the presence of this site change. It is not that you are at the same site so you have data from the site.

MR. SHEININ: I don't follow everything you are saying, Suva. We are talking about a postapproval site change, going to a new site. So the product is not currently being made there so you don't have data already in hand at the new site.

DR. ROY: But the product will be made there at that site.

MR. SHEININ: That's right. It will be made there as will--when we are talking about new NDA, that product will be made at the new site, also.

DR. ROY: But, for a product that is already approved, you are changing from one site to other and the data will be generated at that site because that is the way you can generate the data on the product. But, if you look at ICH Q1A, which says that you can get approval for your product based on data from your R&D batches and other scale batches; correct?

DR. SEEVERS: And we will approve the product and approve the pilot site as the manufacturing facility that is consistent with ICH Q1A. If you wish to add another facility afterwards, you would do that as a postapproval change under SUPAC.

DR. ROY: I think that is not the spirit of the ICH Q1A. I think we need to look at the ICH Q1A. It think it is being read the wrong way.

Let me make one other issue about this site-specific. What we are looking at is stability failures, et cetera, the examples that were given--what you are looking at is the result. You need to look at the cause, why those things happen. If you parse it all down, it comes down to IQ or OQ or PQ validation issues.

FDA is a strong scientific body which looks down deep under to find what is the issue and how to solve it. I think over here we are taking a band-aid approach. It is like saying one reviewer got a traffic violation because he broke down on the highway. So every reviewer will get a traffic violation.

I think that is kind of a ridiculous way of going.

Thank you.

DR. WILLIAMS: Suva, thank you.

I am going to focus in the expert panel to see if there are any particular questions they would like to ask of

the presenters or discuss among themselves. But I would always encourage people from the audience to speak if they have a comment or question.

DR. SEEVERS: I would like to ask Pat Tway and others from industry about the issue of building a new plant and what site-specific stability would do to your time line. How often, for a new drug, do you actually commercialize it in a built-for-purpose facility versus how often do you use existing worldwide capacity.

It sounds to me like this is an extreme case that I would like to know what the proportion is.

DR. TWAY: Right now, it is 100 percent we are building.

DR. SEEVERS: Every new drug you make--

DR. TWAY: Every new NCE which is the longest time line there, if you look at it, the bulk-drug facility, the API facility. Right now, we are in a stage where every new NCE we are going to manufacture, we are building either a grass-roots facility or we are adding on to existing facilities, or we are taking--and this is, actually, right now in the minor case, we are taking existing facilities and doing major renovations which can take up to twelve to fifteen months, gutting them and putting in different equipment, that type of thing.

Basically, and I can only speak for Merck,

obviously--Merck has historically built--historically, now--not flexible facilities. They have built one-by-one as they needed it. We now are trying to build flexible facilities but, basically, all of our flexibly facilities are 100 percent full and chugging. So it is basically, right now, every single product we are doing it for.

DR. WILLIAMS: Pat, thank you.

Eric, you were next?

MR. SHEININ: That was the same question I had. I would like to hear from some other people. I also had one comment. I wanted to emphasize that the tables that we passed out with the revised FDA proposal on site stability that we would be asking for which is, as you know, quite a reduction from what is in the draft guidance.

This is all predicated on the assumption that you would be coming in at the time of submission with the ICH-recommended amount of data, basically twelve months at 25 degrees, six months at 40 degrees, on three batches, two of which would be at least pilot size. So that is something you have to keep in mind.

If you came in and asked to come in as an exception with a fewer amount of data, then this table is not in effect. But, as far as the manufacturing facilities, Pat, it sounded like you were saying you are building a new facility for the drug substance. Did you mean also for the

drug product? What about other companies? What is their philosophy?

DR. TWAY: Drug substance, we are building new facilities or adding on facilities. Drug product, generally, at this point, we are adding new lines. Some of them were building new when it is full new technology, but if it is a standard drug compression, we are frequently, right now--to be honest, we are running at 100 percent capacity as you can tell.

We will be adding a top of the line to a facility and that type of thing, but we do come in with ICH stability and we do have that.

DR. JOSHI: My name is Yatindra Joshi, and I have already given my card before. I think there has been significant consolidation and there has been a significant effort to cut costs over the last five to ten years. So ticops has been a major issue where the costs have been cut down significantly.

Many of us are now finding we are in a situation where we cannot absorb new products and, therefore, you need to expand the facilities or have totally new facilities.

The other thing I would like to add is you also have cases where you have a product which is different from what you have been manufacturing and, therefore, you need equipment. As somebody in the presentation said, there is a

significant investment that is needed.

One product that we are dealing with right now, there is an investment of about $20 million is needed and we are not sure that the product will be successful in the phase III clinical program. Therefore, it is a significant risk that companies do not want to take. But if the product really is demonstrated to be successful in phase III program and can significantly impact the lifestyle of patients, then those patients are at significant risk.

DR. SEEVERS: Let me just reflect on that a moment. If it is a new dosage form for you and for the manufacturing facility you will be putting up, all the more stress on the criticality of tech transfer and process validation and the places where holes can happen.

DR. JOSHI: I think the critical thing is to see if you have characterized your product and your process really well. If you characterize your product and process really well, then all the problems that you presented are resolved. I think it is being said--I think, Steve, you probably mentioned that--as far as the drug substance is concerned, it is really the crystal properties and the properties of the drug substance don't change as you change the manufacturing site.

What could potentially happen is, in terms of impurities, if you have a change in scale. Those could be

different. As our colleague from Merck said, I think those are minor issues. We are talking about impurities levels of 0.1, 0.5 or 0.2. Those are small. So we have got to keep that in mind.

MR. SHEININ: Let me ask, if you are building a new facility for a drug product, at what point would you be ready to undergo a preapproval inspection and demonstrate to the investigator that you have the capability of manufacturing the product at that site. At what point would you be in a position to being making the process validation batches?

DR. SEEVERS: I'm sorry; I don't have the answer. Can somebody else address this question?

DR. MASSA: By guidance, we are supposed to be ready for preapproval inspection at the time of submission. But what that entails is not necessarily having validation lot data. What you have to have for the PAI is a validation protocol and have the appropriate equipment available to be inspected to show that it has been properly installed and is capable of running.

Prior to commercial marketing of the product, we are supposed to have the validation-lot data available if FDA decides to come in and look at it. In some cases, the field does not avail themselves of that opportunity. They come in and do a postapproval look at those data.

I think one of the things you have to be careful of here is that it is not just a matter of going to your local pharmaceutical supplier and taking a filling line off the rack and saying, "I need this installed." A lot of this equipment is long lead time and it is custom made for a particular facility.

So if we have to back that up, we have to make a commitment of the suppliers of that equipment at a much earlier point in time that we need to get that equipment. Even if you are talking about modifying existing equipment, it still runs into the millions of dollars.

MR. SHEININ: I know what the guidance says and, actually, I think, the regulations as well. But what I am asking is, in reality, when does this take place because, given the shorter approval times and shorter development times, we are hearing that it is more and more common when an investigator goes out, the equipment is not even in place in that facility.

So I really want to know how often do you have everything ready to go for an inspection the day you make a submission. It doesn't seem to be across the board that companies are ready for an inspection the day they submit the application to us.

DR. BURTIS: Taylor Burtis from Genentech. I can speak to that from a recent example that we have at

Genentech. We currently have a new bulk facility plant that is on-line. We are going to be manufacturing our call lots beginning in May. Our submission is to go in in August and we expect a preapproval inspection within a 30-day to 60-day window.

DR. EGAN: Actually, I have a question for Dr. Shah and if other manufacturers would like to chime in as well. During your presentation, you gave a large number of examples about transfer of manufacturing from one site to another site and that these transfers did not affect stability, and that it seemed that you had done a fairly extensive survey of these transfers.

During the survey that you took of changing manufacturing sites, did you actually come across any counter-examples where stability was affected and can you provide us with--if I go back to the beginning talk--a numerator and a denominator. And if any of the other manufacturers have conducted some kind of similar survey about transfer, if they could provide some information about numerators and denominators in this process.

DR. WILLIAMS: Dhiren? Is Dhiren here? Sorry, Bill. Good question. No respondent.

MR. LACHMAN: There is one area that I think we have not discussed here. You can have the best validation and best training qualifications and so on, but you need,

also, the best change controls so that changes don't creep into your validated process that could impact your end product that you really are not aware of. So change control is very significant in this whole area.

The other thing is, I just want to mention and this is just for comment sake, is that a lot of innovator companies are outsourcing manufacturing and control. That is going to be something that needs to be considered.

MR. FURNKRANZ: We have heard a lot about adequate process validation and adequate technology transfer results in an equivalent product. Dr. Shah's presentation gave a very good example of what I would consider adequate process validation; multivariate analysis of all of the potential problems that could occur during the transfer.

However, I am not getting the sense that there is adequate process validation or equivalent process validation throughout all of the companies. We had another example of process validation where they basically compared the specifications of pre-transfer versus post-transfer.

Is that a process validation as well and are they adequate. Is there a standard in the industry right now that you can say, "Our process validation is adequate?"

DR. REYNOLDS: I think one important thing to remember is that--I may not have done as good a job as I should have in terms of emphasizing it--is that process

validation does not stand out there alone, that it really has a basis in the development program. So it really important that the development studies elucidate more than just what you would get out of an experimental-design program but that you really have fundamental studies of the stability of the product, the characterization of the process, the controls of the process, and that that fundamental understanding really is the basis of what goes into validation studies.

I think that is really the key issue and, again, as several people have discussed earlier, those issues really are probed very heavily during a preapproval inspection so that information really is discussed at length with the FDA.

DR. SEEVERS: Scott, can I ask you a question in response to that? What effect has the decreased agency review time had on this process? What I am getting at is, just in my own review experience at the agency in the last five years, I have come across three cases where, postapproval, a new polymorph showed up that, in theory, ought to have been picked up in a good development program, that created significant problems for an already approved drug.

My concern is that, as our review time is compressed and your development time is correspondingly

compressed, there is a lot of pressure to get things out in a hurry and some items are being skimped on.

DR. REYNOLDS: I can make a comment from my experience at Merck how we responded to that.

DR. KASUBICK: From another point of view--and I just lost my train of thought.

DR. WILLIAMS: I could make a comment while you are collecting your thoughts. I actually, and the chemists know that I do this--I always try to think what is the question when we talk about this. It seems to me that the question, somehow, is the quality and performance of the product that is intended for market, the same as the clinical-trial material on which your safety and efficacy data were based.

That is a very interesting question and I think we are trying to answer that question with site-stability data. But it also intrudes in my thinking the thought that the performance, somehow, of the bioavailability/bioequivalence of the product has changed with this site change. My understanding is that industry, in approximately 40 percent of the cases, does do bioequivalence studies, say, between the to-be-marketed dose form and the pivotal clinical-trial material where they showed bioavailability.

I don't know if anybody in industry wants to ponder that and then give a comment, but it seems to me

something that is much beyond site stability in terms of a need or an interest.

While everybody is horrified with that question, I will go back to Bob.

DR. KASUBICK: Now I have it back. The point I was going to make is that sometimes it seems that what we are doing here with the site stability is that we are applying a fix across the board when, in fact, what we need to be doing is doing some risk assessment and saying we need to deal with those exceptions and not make it a blanket statement that we have to do it all the time.

Again, I think this goes back to something that PQRI is trying to address and saying what kind of methodology can we put into place so that whatever fix we have deals with the problem and not just a blanket statement.

DR. SEEVERS: I think that the draft proposal that was distributed the other day does try to take a risk-based, tiered approach to say what are the relative risks, what can one expect generally. What we are trying to do is find a way to catch those cases where there is going to be a problem without unduly burdening places where there is less likely to be a problem.

DR. SOLLER: A comment, if I could. Dr. Egan, I don't know that I have an answer for your question. I know

that question was in search of an answer. But I do have a comment and maybe an approach.

Just in talking with some of my colleagues over lunch and during the break, for at least a part of the industry, and I am not speaking for the entire industry at this point, SUPAC may, in part, be a root cause here. As I understand, the issue of the site-specific stability in SUPAC was more of a compromise to avoid preapproval as opposed to something that was a deliberative, scientific process.

That is at least a perception. You can argue that whatever side, but that is at least a perception on one side of the table. Just sort of stepping back and looking observationally at what went on this morning, we seem to have at least one side that says there is little value here. And then there is another side that says there is great value.

We see a numerator of about ten with a question what is the denominator. And we have seen a denominator starting at about 100 or more of what I saw today which gets us down to 10 percent, anyway. Who knows what the numbers are? But it is clear that there is an industry here that is united in opposition or at least in serious question of what is being proposed and possibly even in the reproposal.

There are significant financial and significant

resource and significant time-to-approval issues which are not just company issues but, certainly--time-to-approval--are patient issues as well.

I think I also heard, and have heard from my colleagues on our side, that it doesn't look like "one size fits all" here, that we need to be thinking about, perhaps, a more flexible approach. I take your point that your risk-base analysis was a attempt to get there.

I am not sure I am hearing, today, that, sort of, we are there. I am hearing a real desire on the part of industry for more dialogue, for more data collection, and maybe PQRI can work here, and a concern from industry that the Q1A(R) process be somehow linked in parallel here so that there a true harmonization of what is going on.

Personally, I was taken by part of Dr. Shah's presentation in looking at it from a risk/probability analysis because I think that, among my colleagues, they feel that there are many guidelines that are being used when it comes to tech transfer.

But, in looking at at least the start of that one slide that showed the various points that could affect a tech transfer in trying to itemize and categorize that, there are guidelines that could be put into each one of those and certainly stability is only one of them.

Maybe, looking at it from an industry standpoint,

we are a group that is saying we really are GMP-motivated here, we are process-motivated, we are validation-motivated. That is really where our vision is and that we don't see the site-specific stability as an appropriate marker as to where we are philosophically.

I am not going to predict how the further dialogue, which I hope we have, on site-specific stability will net out. But one approach here that might be helpful to get at some of your concerns that process validation isn't a 100 percent process--which, by the way, I disagree that we have to have 100 percent on, necessarily, anything because there will always be human failures and machine failures and we have to expect that.

But we do have to look at what is operationally feasible and reasonable. One thing to think about, Roger, might be to look at the tech-transfer type of document that would collapse some of these things.

My last point here would just to bring in something totally unrelated to drugs that was a very smart thing that FTC did on dietary supplements and that was, in the face of a wide variety of advertising and recognizing that they had policies that went back many years and guidances that went back many years on how to handle deceptive, fraudulent, unsubstantiated guidelines, they drew all of those together into a document that was specifically

targeted to dietary supplements.

That helped bring awareness to an issue. I think that kind of approach here where we look at the various guidances that companies are using in terms of process validation, other elements a la the Shah model that we saw earlier, that that would bring awareness and would, I think, enhance the comfort level that when tech transfer is occurring that the process validation and knowing the process, knowing the product, is really happening when that occurs.

So, in sum, I think it would be very helpful if we continued this. This 90-day period is going to be extremely helpful. I congratulate you for bringing this to the fore so that we can get things on the table and would urge that maybe there is another type of dialogue that could occur, either PQRI or another meeting like this once that comment period is in.

We certainly will all crystalize our thoughts much more after today.

DR. WILLIAMS: Thanks, Bill. Comments or questions to that from the panel?

DR. SEEVERS: Just one thought. You mentioned that it is unreasonable to expect any process to be 100 percent perfect. I agree with that. Let me tie that together with something that another speaker said this

morning, that what is involved here is shared risk, that the agency risks there being a problem and the company risks a recall which, certainly, is undesirable.

Let me add that the American public shares in that risk because, in this case, what would happen is if there is a stability failure, that drug would have been in the hands of the public for a certain period of time, typically many months. So let's not forget who is sharing the risk.

DR. SOLLER: Oh; I would not forget that at all. In many respects, a credo that often comes forth in our organization is that consumer confidence is our most important product and that confidence comes from making quality safe and effective products. So I would never go away from that, but I am struck by the conversation that went on during the break about the ten examples that you brought up, that these really represent GMP-types of issues, the kinds of things that would occur whether a site change occurred or not.

I think, as you are trying to convince an industry that this is an important problem that requires an added level of regulation, I don't know that the rationale and how you presented it has been done in a way that was convincing. I mean that with all due respect because when you go forward with a kind of change that raises the bar, the way you get people to buy into it is when it is done in a very

convincing and believable way that at least tries to match up where they are philosophically in trying to produce safe, effective and quality products.

DR. SEEVERS: I have to disagree with one thing. This is not raising the bar. As I mentioned in my talk this morning, the 1987 guideline said that site-specific stability would be necessary. We are not changing anything.

DR. SOLLER: I am just looking observationally. Everything I heard today was a perspective of a bar being raised.

DR. WILLIAMS: Bob and Bill, first of all, I think it is a useful dialogue but I see some other people who have been waiting to talk.

MR. ROTHMAN: It is Barry Rothman. I am with the Office of Compliance in CDER. I just had this one comment, and this doesn't say yes or no for site-specific stability, but stability failures are probably the leading cause--if not the leading cause, one of the leading causes--of drug-product recalls each year. Theoretically, these are products that have been validated and manufactured according to GMP. I just wanted to make that comment.

DR. MASSA: Toby Massa, Eli Lilly. I think there is a very fundamental disagreement between how we interpret the 1987 guidance. I deliberately did not get into that today although I felt that there is a regulatory component

to this.

If you read the 1987 guidance, to begin with, for drug substance, it says that the stability profile of a drug substance need be qualified only once per method of manufacturer. It does not say anything about once per manufacturing site.

Any discussion of providing additional data for a change of manufacturing site is restricted, A, only to drug product and, B, only to postapproval changes.

DR. SEEVERS: That is not transfusion. In the guidance, what it says is, under preapproval, is "See postapproval." And the language is exactly the same.

DR. MASSA: I think we have basic disagreement there, Bob. With all due respect.

DR. SEEVERS: We can read it together later.

DR. MASSA: I definitely think this is an increase in the bar because, also, if you look at what is there, it says, "Up to three months' data may be required depending on the product type, depending on the stability history." What we are talking about in the stability guidance and the alternate plan that you just put forward, in some circumstances, we are looking at more than three months data so this is an increase in the bar.

DR. BYRN: I just wanted to ask a question related to the public-health issues. We are hearing from what you

would call the most conservative, most cautious companies, today. Is it across the board? Is the extent of process validation, tech transfer, et cetera, the same level that Merck and Lilly and so on apply or is there an issue related to other companies that we are not hearing from?

That is a general question for the industry.

DR. WILLIAMS: Or the review staff. Is there an uneven character to the kind of validation?

MR. SHEININ: We don't normally see the process-validation data. We do get sterilization validation data for a sterile product but the other data are not part of the submission. They are reviewed by the investigators.

DR. WILLIAMS: Let me just ask a quick question here. When we say process validation, are these the validation of the three production batches? Is that what we are talking about?

MR. SHEININ: Yes. That is a GMP issue.

DR. WILLIAMS: I always have to turn to Barry to say, "What does that really mean," but my understanding is you make it the way--you are sort of making it three times to see if it meets the specifications. Am I saying it right, Barry?

MR. ROTHMAN: It is an insurance that your process will consistently produce a product that meets a set of predetermined specifications.

DR. WILLIAMS: You don't have to really vary the parameters of your process, do you?

MR. ROTHMAN: No; it shouldn't be varied. It should be set in advance and you are just assuring yourself that you are capable of meeting those parameters.

DR. BYRN: But Merck is also saying, for example, that they do--and I know it is true. All these companies that are speaking here do a ton of work outside the lines, if you will, to understand what is going on.

DR. WILLIAMS: I don't want to hold up the questions because I see a lot emerging, but what I think of when I think of this kind of very sophisticated scientific exercise is where people are kind of varying certain parameters to show that they still have control of the manufacturing process to yield a good product.

Now that is very different, in my mind, from what Barry just said.

MR. LACHMAN: Just a clarification on the process validation. If you have a range and if you have a set point, let's say in the middle of the range, if you are doing three batches, you should cover the range, the lower and upper and the midpoint and not just one point of that range.

DR. WILLIAMS: In terms of--

MR. LACHMAN: The validation.

DR. WILLIAMS: Of the parameters that control the process.

MR. LACHMAN: Right.

DR. DEVINE: Rebecca Devine. I am with the Center for Biologics, FDA. I just wanted to point out that there is a slight difference between some of the traditional biological products in terms of the process-validation information and when that is available.

It is not the same situation as for a drug product, say an oral-dosage form. For biological products, we expect the process validation data to be in the original application for the consistency batches because part of our concern is that many of the products are not characterizable and they are very process-driven.

But I believe that is also the case for the sterile dosage forms for drugs in CDER, and CDER can correct me if I am wrong, that the validation data on the batches for sterilized dosage forms has to be in the original application.

So, in terms of timing issues, I think things have been a little bit different for the biological and sterile dosage forms.

DR. EGAN: I just want to add one further thing to that, coming back to your question about unevenness of quality of validation. Even to the extent that that exists

throughout the industry, it is actually incumbent on us to review that and, if we are not satisfied with the validation, to say so. So I think that is the standard there.

DR. JERUSSI: I am Bob Jerussi from Jerussi Consulting. I just wanted to respond to Barry Rothman, if I might, Barry. The main reason for recalls for stability is dissolution. If you look at it, that is what it is. The agency, itself, has called dissolution testing a more discriminating test than bioequivalence or bioavailability. I don't know how much weight to put in that.

What we are doing today on recalls is we are recalling batches that are probably bioavailable and junking them. That is a terrible waste. We shouldn't allow that to happen.

Secondly, I would like to mention--I am a member of the Organic Division of the American Chemical Society. I just received my booklet called Organic Synthesis. They are limited to four-step syntheses. Anyone can submit them, but they are checked by a group of checkers. That is called a validation.

The checkers, then, make recommendations to the submitters and they finally publish it. Now, you can make that chemical entity in any lab anyplace in the world. As I said in June, the molecule doesn't know where it was made.

DR. KASUBICK: Just a comment on Leon's comment about the ranges during process validation. Any time that there is a variable that you take a look at, if it is a temperature or whatever, the particular measuring device that you use determines what that range is.

So if you employ it and say you are going to run a 25 plus or minus 2, or whatever your indicator will give you, then that defines what range is acceptable. You don't, necessarily, have to look outside of that range. You just simply have to verify that, in fact, your equipment will operate within it.

It is quite possible that, even though you are operating within a plus or minus 2 range, plus or minus 5 might be very adequate and still give you same process. So it is the accuracy of your measuring equipment that determines what your ranges are going to be in general.

DR. ZIMMERMAN: I am Stewart Zimmerman with the FDA, Cardiorenal Drug Products. I attended the seminar yesterday and what Toby was mentioning--there is variability with respect to SOPs all over the map. We don't see that, but that is one concern that you brought up, as to variability effects.

That was a pretty significant thing in this whole thing, so I was just wondering how that weighed in, or maybe they could even have a separate workshop dealing with that.

I don't know to what extent compliance deals with this issue, but I don't see any of this as a reviewer.

DR. JOSHI: I am going to address the question. Yatindra Joshi from Novartis, again. I think Scott has said that very well. Before even we go into validation at the time when the formulation is identified, there is an incredible amount of work that goes in to determine what the process is, what the critical parameters are. Any time a change of scale occurs, then defining how these critical parameters impact.

And then we go after that, really, into validation. So there is an incredible amount of work that is done to make sure that the process is robust and it is yielding a product with attributes that are desirable.

With that comment, actually the question that comes to my mind is--Roger you had asked if you had seen the validation data. I am just wondering if the center does not see the validation data, do they really have a good knowledge of how much work is put in, and so this question about whether the site-specific stability is needed, do they have a good assessment of whether that is a fair question or not.

And then I go back to the first comment that I made. FDA has more information than any one of us has because you have looked at all the products. There is a

requirement for registration stability which is generally done at a different site. Even during development, for global organizations, Novartis included, products get made, manufactured in two or three different clinical facilities.

So we have all that experience. And then definitely commercial stability is done at commercial sites. If you look at large pharmaceutical companies, these products are made in so many different plants globally.

And then, as one of the presenters talked about captopril, twenty-two different generics, it is a sensitive drug substance. You have more information than you could ever have. If you look at the information, what you will find is there is--in most cases, the registration stability is comparable to the commercial stability and, therefore, I think we already have an answer to address this.

MS. MALIK: Just to maybe provide some additional clarification. At least from the HIMA standpoint, we are committed to stability at each of the manufacturing sites. I think the question and the basis of the discussion is what are the primary things that you look at and are the predictors of the quality of that product.

I think that is where we feel that--it is the process validation, but I don't think we are making the point that it is process validation alone. Again, to come back to what Scott said, it is the entire understanding, the

technical understanding of that product, the technology transfer as well as the process validation.

But we are committed to doing the stability. I think we are talking timing. We are talking what is a primary indicator here. And, again, looking at this experience base--if we really look at that, I think, as I indicated in my presentation, we have not seen any case where there is a difference, a change in stability simply due to the manufacturing site change and of looking from an agency and an industry standpoint and making sure we understand that.

Thank you.

MR. PATTERSON: Hello. My name is Nate Patterson. I am with Chiron Corporation. At the AAPS meeting, this handout was put out by FDA, this draft handout. At the bottom, there is a note for, "biotechnological products data from accelerated stability studies are not required." In today's handout, that same note is missing.

My question is the origin of the note at the bottom, the asterisk, in the first place and also why it has been removed.

Thanks.

DR. WILLIAMS: We did comment on that briefly this morning. Does anybody want to comment from the expert panel or the committee?

MR. FURNKRANZ: We had discussed this between CBER and CDER and CBER had indicated that, for products submitted to CBER, that accelerated stability studies were not necessary. We put it on and there was going to be discussion between CBER and CDER how the feelings were with regard to whether that is or isn't necessary.

These tables were put out even though we had not resolved that issue. As a result of some discussions, we felt it was appropriate to take that off for the present time and discuss that internally. So that is why it was on there, but it wasn't intended to go out. We have made the corrections.

Please utilize the ones that were submitted today.

DR. WILLIAMS: I am not trying to put anybody on the spot, but Larry and Garnet, there is an academic perspective here that we value very highly. So if you want to add anything, please feel free to do so.

DR. PECK: We have got 35 minutes. I have been reflecting here on what has been said, and you don't trust an academic with a microphone. It can be very dangerous.

But I will try to be brief and say something that will undoubtedly offend somebody and probably be told, "You don't know what you are talking about." We have been in academics but we have been elsewhere, too.

You need to reflect upon how a product is evolved.

A product comes from an R&D function and we assume, in today's climate, that the R&D function does all the necessary studies of the active moiety plus those materials that are going in to combination with that moiety.

We are assuming that we have--at least, I am hearing part of this--we are assuming that we have characterized that drug substance very well and it is not going to change and no differences are going to appear as we now evolve the product.

If you believe that, I can tell you anything, then, because there are things that are changing. Someone doesn't necessarily want to believe in polymorphism, but that is a thing that is very interesting, has created a rather interesting research group in San Juan, Puerto Rico, at the university. And that group is servicing our industry on the island looking at this.

We move from R&D and well-characterizing the substances that we are going to put into a dosage form and we have those scientists that evolve the dosage form. They have been given a lot of scientific information to do this evolution.

We are now starting seriously into something called stability. Once we start into the product, and we are gathering a lot of information. We are also gathering information about the processing. This is before we have

gone into clinical work. We do batch sizes of a number of different sizes to understand the product. A lot goes on there.

Then we finally get into the clinical study doing phase I where the dosage form may be very simple and then start increasing not only the complexity of it but the batch size. So we go through the clinical studies and, especially in phase III, we enlarge these studies and we are looking at the process. We are insuring that we are going to evolve the best process.

I would be interested to know if there is an estimate as to the number of batches of a new drug entity that have been put together by the time the product is ready for technology transfer. Technology transfer is a tough area. If you want to put a conference together and have a symposium on tech transfer, you can do it almost every year.

I wonder if there is a standard methodology for tech transfer as we talk about other things. Through all of this, we are evolving information for validation because validation is not based upon just what we do at the end. We have built it up. So we move along through the validation process but that is not the whole story.

Unless we have adequate specifications for what is going into the product, we have a tough time with validation because it may fail. Finally, transfer into manufacturing,

there may be adjustments there. By this time, we have at least looked at three major batches for the validation process and we feel comfortable.

The stability picture may vary. There is always a concern, and some people may not have experienced this. Dhiren Shah showed that they had many products that had no problems. But there is always a possibility and I guess there is a conservative nature here to make sure we keep a handle on stability.

But, again, we have to make some decisions based upon the overall picture as to how much stability data we need. You will have experiences, and it was very fortunate for us today to have heard some actual experiences that companies have had with their particular products and the good stability profile.

I am not going to comment yes or no about the magnitude of stability, but we have to realize that there is a huge building block here and we come to the end, and then we market a product. It has to be safe for the public.

DR. WILLIAMS: Garnet, thank you for that very useful overview. Larry, some further thoughts?

MR. AUGSBERGER: Do I get thirty-five minutes, too? I won't need that much time, but I will make a quick couple of comments, though, Roger. I think that this has been an extremely interesting experience for me to have

listened to all the comments and the formal presentations that members of the industry have made.

Obviously, there is a high degree of development and validation and tech transfer expertise displayed in those presentations. That is really comforting. I think that the limited--I will say limited--examples that we saw that were submitted as part of these presentations do suggest that site-specific stability can be managed by those processes.

But I want to come back to a question that I heard raised before and is still in my mind, and that is, does that expertise and commitment--obviously commitment is part of that--exist across all the firms in our industry. I am also sensitive to the timing issues of when site-specific stability data will be needed. I really do understand that problem but I am not quite sure how to manage that, particularly if there is any doubt about the fact that some of us are not quite committed to good practices of development and validation and tech transfer as others are.

But I am willing to be convinced by the data. While we are talking about data--this may take thirty-five minutes--while we are talking about data, a number of persons today bounced the letters PQRI around. Maybe I am wearing my PQRI and AAPS hat this morning, but I think that there is a value in remanding some of the questions to

systematic research or study or data mining or whatever the case may be, and PQRI is the place to remand that work.

But I will have to say, and pardon me for saying this, but show me the money because one of the things that PQRI is going to need is a lot of support from industry in order the mount those kinds of research efforts.

Also, while we are talking about data, I heard one comment that the main failures of site-specific stability appear to be dissolution. I wonder how many of us really understand the nature of dissolution and the physical processes that are involved in that. What is the relevance of accelerated stability as a predictor of changes in physical processes? I think that is a question that needs to be looked at.

DR. WILLIAMS: Larry, thank you very much.

We are in our last twenty-five minutes. I have some wrap-up statements, of course, but I think I will turn now to the audience and say, "Are there any last-minute comments or questions?"

If not, I will turn to the expert panel and ask the same. Any last-minute clarifications or questions?

DR. BYRN: One issue that was brought up briefly at the academic meeting and hasn't been discussed, but Larry mentioned it, was timing and whether or not site-specific stability data could be submitted during the review process,

after submission but before the PDUFA date and whether that is an issue which should be explored further or not.

I thought that was Pat Tway's proposal but I don't think it is on further discussion. But is that an approach that would, in cases--is that a compromise that could be achieved or is that something that industry is not interested in?

DR. WILLIAMS: Maybe I will turn to the agency people. Any thoughts about that--because my understanding is it would not be stability data, it is validation data.

Bob, do you want to comment on that?

DR. SEEVERS: Pat's proposal was validation data as I understood it. I would just point out that, in table 1 of our proposal, that is exactly what we suggested in cases of moderate potential to have an impact. That is exactly what we were proposing.

DR. WILLIAMS: Expert panel; anything more?

DR. PECK: It was impressive again this morning to hear Dr. Shah give examples of many of their products. I don't know if this is possible to get further information similar to his appropriately blinded, or whatever, just something to look at and to reflect upon. That would be very helpful.

DR. WILLIAMS: Thank you. And I think, Bill, you suggested that, too. I was keeping track of the numerator

and denominator, too. I got about 10 over 100, or maybe a little more. I think we all agree that that kind of data is quite valuable.

I will turn to the people from the agency. Any other comments or questions?

DR. SEEVERS: Just one thought. My discussion a few minutes with Toby about the correct reading of the 1987 guideline suggests to me the importance that the agency places on coming to some sort of consensus, if not happy ending, with industry on this issue because we are committed to the ICH revision process. We are devoting a fair amount of resources to that.

However, we ended up in guidance limbo for the last thirteen years, in large measure because we decided to wait for ICH before revising the domestic guidance. The time has come to finish that revision. If we remain silent on this issue, then the very dispute that Toby and I had will remain open until such time as ICH speaks and I think we can all expect that to be not this year and probably not next year with any sort of finality.

What we need to do is find a workable approach to this, something that we can all live with in the interim. The last thing we want to do is leave this unsettled.

DR. CHEN: Chi Wan Chen, FDA, CDER. I would just put in a plug for that, too, because I am representing CDER

on the ICH Q1A revision. I has said to the ICH Q1A Revision Expert Working Group that the best thing, in terms of the site-specific stability issue, is for the U.S. industry to continue a dialogue with FDA while recognizing that this issue is on the drawing board for Q1A revision.

With this continued dialogue, we are going to, hopefully, finally come to some resolution and some mutual understanding that we can feed back into the Q1A revision process. Otherwise, the Q1A Revision Expert Group will work from a vacuum. So I hope we can continue this dialogue.

MS. EASTER: I am Carol Easter and I am representing the PhRMA Stability Technical Working Group and I, too, am part of the Q1A revision process. Basically, what I wanted to say specifically to Bob and to the folks that went to the trouble of collecting the ten examples that you have given us today, because we have been asking for the last two years to have the data to back up the concern from the FDA regarding the site-stability issue.

I looking over this briefly, I can only find one example on those ten that appears to actually relate to--if you had three months of stability data, that you would have caught this problem. That is the way it looks to me. I would have to go over the data more carefully, what you have given us in your slides.

But there is one that says at the two-month

accelerated time frame, you found a problem. In that one out of ten cases, you would have possibly caught a problem. What we are still not sure of is the root cause. Was the root cause really the site? Was it a GMP problem? Was it a packaging problem? Or what were the other problems?

So I would challenge FDA and I will go back with my Stability Committee and also see what kind of information we can find, not just situations that may have been totally successful. We will see if we can find some folks that will admit that they may have had a problem as they went from the pilot to a final site, and then we will go through and try to find out what the root causes were.

I am sure, if we can come back and prove to everyone that site is the controlling factor, we will be able to go forward. Personally, with thirty years of experience in this industry, I believe we are going to find all the things that have been enumerated here today, that there were people who did not have their processes under control, did not do their appropriate validation.

I think what the FDA really--I hope that they are hearing today is that there are appropriate ways to control these things. Site-specific data are always generated, three batches always committed to for the innovator industries.

What we are talking about is trying to plug up

something with the wrong band aid, I believe.

Thank you.

DR. WILLIAMS: Thank you for that very interesting offer, I guess from the PhRMA Stability Committee?

MS. EASTER: Yes.

DR. WILLIAMS: To consider. I know there is no commitment now in these kinds of meetings.

Further comments? If not, then I think we have done very well in terms of our time. We are a little early, fifteen minutes, and I would like to make some closing comments.

I have been sitting here drawing pictures of boxes and arrows so I can track what is going on. I would like to say a few things, probably about three minutes worth of words, now, as we close. I think there is kind of a time line going on here where we are now March of '99. We are going to close comments in June of '99.

I suggested that we consider another meeting of this expert panel somehow in connection with the receipt of those comments. I am not making any commitments now. I am just offering thoughts for us to consider when we get back to the ranch.

October '99 is the ICH meeting in Washington where we will continue under--Chi Wan, I believe you are our leader for that effort--to work on those twelve or so

additional ICH topics that you discussed in the workshop. I do have the thought, and now I will speak with my preference, that we would like to finalize the domestic guidance recognizing that it will be updated and modified based on the ICH progress.

Eric and Frank, isn't that our intent? I think it is useful to have the domestic guidance. Now, of course, in finalizing that guidance, we will come to the key bridge to cross which relates to site-specific stability. I take the point of Bill and many others that we need this useful kind of dialogue to come to something that, hopefully, we can all live with and that is data driven and scientifically appropriate and that recognizes the public-health issues as well as the needs of industry and their very rigorous time lines.

So that is kind of a hint at where I see us going from here. Did you want me to say a little bit more about ICH? I think ICH, we are very sensitive that we have to interdigitate the ICH effort with our progress on the domestic guidance.

One of the things I would like to say, in starting out, is this has been a difficult issue but I don't want the focus on this issue to cloud the really remarkable progress we have made. If you look at the domestic guidance and the ICH effort, I am just astonished that we have come as far as

we have in the last seven or eight years.

I think we are--and I hesitate saying this, but I do have the dream in the next couple of years that we will straighten out stability. I used to think stability was forever, but somehow I think stability can be straightened out and that we can come to a good consensus on how to do it.

If you ask me to give a percentage, I would say we are 80 to 90 percent there. I don't want to appear too naive, but I would like to think that this is our last major hurdle, the hurdle of site-specific stability. I know I am going to be proven wrong having said that, but I think it is, perhaps, the major debate that we have to engage in when we come to our closure on stability. I like the thought of closure.

I am delighted with the suggestions for offers of data and I really thank the people here who came today and talked about their data. I know how difficult that is for industry and I am also very appreciative of the people who spoke about PQRI and the opportunity there to get data that would support our public policy.

You all know that that is the dream and I look forward to the reality. Larry, I am glad you asked for money because I couldn't do that. I would get in trouble if I asked for resources.

In closing, I do want to thank everybody who came from industry and the public. I think it has been a terrific discussion. I think these kinds of interchanges are extraordinarily useful. It is a lot of work on everybody's part to come, give overheads, get the consensus in back of those overheads if you are speaking on behalf of a trade association.

So I do really appreciate it and I know the other members of the agency and the expert panel appreciate it as well. So thank you all for speaking up and coming and sharing that information with us.

I would certainly like to thank the expert panel. It has been a terrific panel to work with and I look forward to the continued dialogue with this panel in the coming months. I think it is a terrific opportunity to continue the dialogue.

Last, but not least, I will thank all my agency colleagues who gave up, from their very busy schedule, to be here and help on this. So it has been a terrific effort.

Now, with that, I will adjourn the meeting. Thank you all and I wish you a safe and pleasant journey back to your homes and offices.

[Whereupon, at 1:50 p.m., the meeting was adjourned.]

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CERTIFICATE

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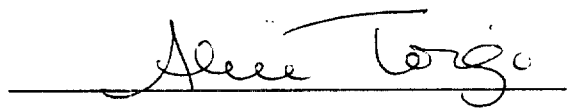

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